Subject: Provenge (Sipuleucel-T)	**Original Effective Date:** 10/26/2011
Policy Number: MCP-105	**Revision Date(s):** Q3 2019
Review Date(s): 12/16/15; 6/15/2016; 3/21/2017; Q3 2020	
P&T Approval Date: Q3 2019, Q3 2020	

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP document and provide the directive for all Medicare members.

Contents

SUMMARY

This policy addresses **Provenge (Sipuleucel-T)** for the treatment of *asymptomatic* or *minimally symptomatic* **metastatic castrate resistant (hormone-refractory) prostate cancer.**

Molina Healthcare reserves the right to update this Policy to include or omit any off-label condition(s) as necessary based on medical literature and clinical studies that may become available.

Prostate Cancer

- The leading cause of non-skin cancer in the US, and the second leading cause of cancer worldwide; Incidence of prostate cancer increases with age and the median age at diagnosis is 67 years
- Four distinct phases of progression: 1) localized, 2) recurrent, 3) metastatic, and 4) hormone-refractory disease. Not all men will progress through each phase as prostate cancer is typically slow growing and may not progress to a life-threatening disease during a patient's lifetime.
- Prognosis depends primarily upon the disease burden at diagnosis.
- Treatment choices for localized or recurrent prostate cancer are active surveillance (watchful waiting), radical prostatectomy, radiation therapy, and hormone therapy
- The choice of therapy is generally based upon patient factors include as tumor characteristics, the site and extent of disease, rate of disease progression, risk of recurrence, symptomatology, comorbidities, life expectancy of the patient, and contraindications.
- Hormone therapy for prostate cancer is also known as androgen deprivation therapy (ADT). It may consist of surgical castration (orchiectomy) or medical castration. Agents used for medical castration include luteinizing hormone–releasing hormone (LHRH) analogues or antagonists, antiandrogens, and other androgen suppressants. Androgen deprivation is considered the primary approach to the treatment of metastatic prostate cancer. However, ADT has been found to be palliative, not curative.
- Prostate cancer cells express several tumor-associated antigens that can serve as targets for immunotherapy, including prostatic acid phosphatase (PAP), prostate-specific antigen (PSA), and prostate-specific membrane antigen (PSMA).

IMMUNOTHERAPY FOR CASTRATION-RESISTANT PROSTATE CANCER

Provenge (Sipuleucel-T)

- Sipuleucel-T was the first autologous cellular immunotherapy to be approved by the US FDA and the European Medicines Agency (EMA) for the treatment of asymptomatic or minimally symptomatic, metastatic castrate-resistant prostate cancer (mCRPC).
- Sipuleucel-T is manufactured from a patient’s own immune cells. These cells are removed by leukapheresis and sent to a processing facility, where they are enriched for peripheral blood mononuclear cells, which include antigen-presenting cells (APCs), T cells, B cells, and natural killer cells. The cells are then cultured with PA2024, a fusion protein combining granulocyte macrophage colony-stimulating factor with prostatic acid phosphatase (PAP). This leads to activation of APCs. The resulting product is sipuleucel-T, which is returned to the clinic where it is administered to the patient by intravenous infusion. In a full course of therapy, this process is repeated for a total of three treatments at two-week intervals.
- Prostate cancer cells express a number of tumor-associated antigens that can serve as targets for immunotherapy [i.e. prostatic acid phosphatase (PAP), prostate-specific antigen (PSA), and prostate-specific membrane antigen (PSMA)]
- Sipuleucel-T is designed to target prostatic acid phosphatase (PAP), a protein almost exclusively expressed in prostate tissue (found on approximately 95% of prostate cancer cells); this treatment approach aims to specifically focus on the immune response to prostate cancer.

Clinical Evidence

- The FDA and EMA approval of sipuleucel-T was based on efficacy and safety findings from three phase 3 clinical studies (N=737 total): D9901, D9902A, and Immunotherapy Prostate Adenocarcinoma Therapy (IMPACT).
    - Patients enrolled in these clinical trials all had androgen-independent metastatic prostate cancer, were asymptomatic or mildly symptomatic
        - Inclusion criteria required radiologic evidence of metastasis, a serum testosterone <50 ng/dL, an expected survival of at least three months, and in good physical health characterized by Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, had tumors with positive staining for prostatic acid phosphatase and did not require narcotics for cancer-related pain. Exclusion criteria included visceral (liver, lung, or brain) metastases, moderate to severe prostate cancer-related pain, and the use of narcotics.
        - Patients being treated with a gonadotropin-releasing hormone (GnRH) agonist at enrollment were continued on it during therapeutic vaccine treatment. Patients assigned to the placebo were allowed to cross over to sipuleucel-T if progressive disease developed.
    - Based on FDA's integrated analysis of these 3 trials, median overall survival was 3.9 months longer with sipuleucel-T (25.4 months, HR 1.36, 95% CI 1.14 – 1.63, p=0.0009) than placebo (21.5 months).
    - Treatment with sipuleucel-T was generally well-tolerated in all three randomized trials. Side effects were related to the infusion of the therapeutic vaccine, were mostly grade 1 or 2, and usually resolved within one to two days. [Higano CS, et al. 2009; Kantoff PW, et al. 2010; Hall SJ, et al. 2011]
- Sipuleucel-T compared with placebo statistically significantly improved overall survival but not time to progression in patients with asymptomatic or minimally symptomatic, castration-resistant, metastatic prostate cancer in the randomized, double-blind, placebo-controlled, multicenter Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) study (n=512) [Kantoff PW, et al. 2010] and in patients with asymptomatic, hormone-refractory, metastatic prostate cancer in a pooled analysis of 2 double-blind, placebo-controlled, randomized, phase 3 clinical trials (n=225) [Higano CS, et al 2009].
    - Overall survival was the primary endpoint in the phase III IMPACT trial. At a median follow-up of 34 months, patients assigned to the sipuleucel-T therapeutic vaccine had significantly improved overall survival (median 25.8 versus 21.7 months, HR 0.78, 95% CI 0.61-0.98). Differences in survival could not be accounted for by variations in subsequent treatment. As in the phase II trials, progression-free survival was not significantly prolonged (14.6 versus 14.4 weeks), and there were no significant differences in changes of serum prostate-specific antigen (PSA).

- All three studies are also consistent in demonstrating that sipuleucel-T treatment does not delay time to measurable progression of disease. In all studies, many patients had further chemotherapy treatment at the discretion of their physician. The survival benefit accrues in the context of additional treatment as needed for symptomatic recurrence.

- No trials have compared sipuleucel-T with over conventional chemotherapy or other therapies for hormone-refractory metastatic prostate cancer.

FDA INDICATIONS

Prostate cancer, metastatic: Treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant (hormone-refractory) prostate cancer

Available as: bag, 250 ml Sipuleucel-T, Suspension for injection

FDA Approved: April 29, 2010

Black Box Warnings: None at the time of this writing

REMS: None at the time of this writing

Warnings/Precautions
Thromboembolic events: Deep venous thrombosis (DVT) and pulmonary embolism occurred following sipuleucel-T infusion (post-marketing reports), usually in patients with multiple risk factors for thromboembolism. Use with caution in patients at risk for thromboembolic events.
Vascular disorders: Cerebrovascular (hemorrhagic and ischemic stroke) and cardiovascular events (myocardial infarction [MI]) have occurred; transient ischemic attacks have been reported following infusion (post-marketing reports). Such events usually occurred in patients with multiple risk factors for cerebrovascular or cardiovascular incidents.

Prescribing and Access Restrictions: Patients may receive Sipuleucel-T at a participating site. Physicians must go through an in-service and register to prescribe the treatment; patients must also complete an enrollment form. Information on registration and enrollment is available at 1-877-336-3736.

CLASSIFICATION: Cellular Immunotherapy, Autologous

COVERAGE CRITERIA FOR INITIAL AUTHORIZATION

Provenge (Sipuleucel-T) may be authorized for initial therapy for members who meet **ALL** of the following criteria with clinical documentation **[ALL]**

1. **Prescriber specialty [ONE]**

   - ❒ Prescribed by, or in consultation with, a board-certified oncologist or a urologist

2. **Diagnosis/Indication [ALL]**
   Documentation of diagnosis required and may include clinical notes from the member's medical records including any relevant labs and/or tests, supporting the diagnosis. Submit all relevant clinical documentation at the time of the request.

   - ❒ Diagnosis of metastatic castrate resistant prostate cancer (mCRPC) resistant/refractory to standard hormone treatment

   AND
   - ❒ Histologically confirmed adenocarcinoma of the prostate with radiologic evidence of metastases to soft tissue, lymph nodes or bone

   AND
   - ❒ A serum testosterone level of less than 50 ng/dl

   AND
   - ❒ Evidence of progressive disease after surgical or chemical castration (known as castrate-resistant, hormone-refractory, or androgen-independent prostate cancer), adapted from PSA Consensus Criteria (Bubley, et al., 1999), showing progressive measurable disease, worsening disease on bone scan, or an increasing prostate- specific antigen (PSA), as defined by **1 or more** of the following: [AT LEAST ONE]
     - ❍ Progressive measurable disease, as evidenced by changes in size of lymph nodes or parenchymal masses on physical examination or radiographic studies;

     - ❍ Bone scan progression, as evidenced by one or more new lesions or increase in size of lesions (not including "flare" that occurs at commencement of hormonal therapy or chemotherapy);

     - ❍ PSA progression: Evidence of progression by two sequential rising PSA levels obtained 2-3 weeks apart or other evidence of disease progression, wherein the PSA measurement is a minimum of 25 percent greater than the reference value or an absolute-value increase in PSA of at least 5 ng/ml over the reference value

   AND
   - ❒ Serum prostate-specific antigen (PSA) level of 5 ng/ml or more

AND

❒ Asymptomatic or minimally symptomatic AND no use of narcotics to manage prostate cancer-related pain. Confirmation/documentation by Prescriber required.
NOTE: Review member's medication profile for use of narcotic drugs within the past 21 days

- *There are no data on the effectiveness of sipuleucel-T in men whose only evidence of disease is an elevated PSA or in those with symptomatic metastatic disease. Thus, its use is restricted to patients with slowly progressive disease, where a relatively rapid response to treatment is not required.*
- *Treatment is contraindicated in patients who are on steroids or opioids for cancer-related pain, and it should be used with caution in patients with liver metastases.*
- *In the clinical trials the term "minimally symptomatic" was defined by a lack of a requirement for opioid analgesic within 21 days of registration into the trial or the lack of an average weekly pain score of ≥ four on a 10-point Visual Analog Scale in the pain log used in the trial.*

AND

❒ ECOG performance status scores of 0 or 1

- *Scores of 0 or 1 indicates high performance status, or the ability to either carry on all pre-disease performance without restriction or the individual is ambulatory and able to perform work of a light or sedentary nature (e.g., light house work, office work). Reference page 12 'Definitions' section for more information on ECOG performance scores.*

AND

❒ No visceral metastatic disease (liver, lung, or brain metastases), pathologic long-bone fractures, or spinal cord compression
- *Treatment with sipuleucel-T in patients with visceral metastases and spinal cord compression were not included in the study demonstrating efficacy.*

3. Age/Gender/Restrictions [ALL]

❒ Adult men (18 years of age and older)

AND

❒ Life expectancy of 6 months or greater

4. Conventional Therapy/Concurrent Therapy/Other Requirements [ALL]

- ❒ "Hormone refractory" prostate cancer (*also known as castrate-resistant or androgen-independent*) defined by treatment by **ONE** of the following. Documentation required: **[ONE]**
  - **1)** Surgical (bilateral orchiectomy) castration*;* OR
  - **2)** At least three (3) months of chemical castration (luteinizing hormone releasing hormone (LHRH) agonists or antagonists)
    - ❍ LHRH agonists (analogs) include: leuprolide (Lupron, Viadur, Eligard), goserelin (Zoladex), triptorelin (Trelstar), and histrelin (Vantas)
    - ❍ LHRH antagonist that is thought to work like LHRH agonists include: Degarelix (Firmagon)

    AND

    For members treated with chemical castration, serum testosterone must have been less than 50 ng/dL at initiation of chemical castration

AND

- ❒ Dates of all previous treatments with sipuleucel-T (Provenge) and planned dates of future leukapheresis, and reinfusion of the Sipuleucel-T (Provenge)

  NOTE: The Prescriber or treating physician to determine the schedule for cell collection and Provenge injection, which must be submitted with request. The timing of cell collection in relation to Provenge infusion is critical because if an infusion appointment is missed, then the prepared infusion cannot be used in the future.

AND

- ❒ The following treatments will **not** be given within 28 days of starting sipuleucel-T (Provenge)
  - ❍ Systemic corticosteroids
    - *Use of inhaled, intranasal, intra-articular, and topical steroids is acceptable, as is a short course (i.e., ≤ one day) of corticosteroids to prevent a reaction to the IV contrast used for CT scans*
  - ❍ Non-steroidal anti-androgens [e.g., abiraterone acetate (Zytiga), apalutamide (Erleada), bicalutamide (Casodex), enzalutamide (Xtandi) flutamide, nilutamide (Nilandron)]
  - ❍ External beam radiation therapy or major surgery requiring general anesthetic
  - ❍ Any other systemic therapy for prostate cancer including secondary hormonal therapies, such as megestrol acetate (Megace), diethylstilbestrol (DES) and ketoconazole. Medical castration therapy is not exclusionary.
  - ❍ Immunosuppressive therapy
    - *Concurrent use with immunosuppressives (e.g. corticosteroids) has not been studied; May diminish the therapeutic effect of Sipuleucel-T. Carefully evaluate for appropriateness of reducing or discontinuing immunosuppressive agents prior to treatment.*
  - ❍ Chemotherapy other immunotherapy or radiation therapy concomitantly with the sipuleucel-T (Provenge)
    - *Concurrent use with chemotherapy has not been studied.*

- *Provenge stimulates the immune system, and using immunosuppressive agents at the same time may alter the effectiveness 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.*

❍ Treatment with any other investigational product or experimental agents
❍ Metastatic disease expected to be in need of radiation therapy within four months

5. Contraindications*/Exclusions/Discontinuations

**There are no contraindications listed in the manufacturer's labeling at this time.*

Authorization will not be granted if ANY of the following conditions apply [ANY]

❒ Non-FDA approved indications
❒ Known hypersensitivity to Provenge (sipuleucel-T)or any ingredient in the formulation; Prior intolerance or allergic reaction to requested medication

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP is included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

REAUTHORIZATION /CONTINUATION OF THERAPY

Coverage of Provenge (Sipuleucel-T) is limited to a single course of therapy consisting of three (3) infusions per member lifetime. Provenge (Sipuleucel-T) may not be authorized for continuation of treatment.

Repeat treatment in individuals who have received Provenge (Sipuleucel-T) previously is not supported by compendia and not considered not medically necessary.

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

Consult the manufacturer's labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and monitoring.

1. Recommended Dosage

Prostate cancer, metastatic

- ❒ IV: Each dose contains ≥ 50 million autologous CD54+ cells (obtained through leukapheresis) activated with PAP-GM-CSF; administer doses at 2-week intervals for a total of 3 doses

  - *In controlled clinical trials, the median dosing interval between infusions was 2 weeks (range of 1 to 15 weeks); the maximum dosing interval has not been established.*
  - *Treatment delays: If unable to receive a scheduled reinfusion, an additional leukapheresis procedure may be required prior to continuing a course of treatment.*

2. Authorization Limit [ALL]

- ❒ Quantity limit: One course of therapy; a three (3) complete doses/infusions per lifetime
  NOTE: Administration of more than 3 complete doses of sipuleucel-T is considered experimental and investigational.

- ❒ Duration authorization: Infusion may be performed up to 4 months (16 weeks) from time of authorization

3. Route of Administration [ALL]

- ❒ Autologous Cellular Immunotherapy for Prostate Cancer is usually an outpatient procedure which is only eligible or coverage as an inpatient procedure in special circumstances including, but not limited to the presence of a co-morbid condition that would require monitoring in a more controlled environment such as the inpatient setting
- ❒ Refer to MHI Policy & Procedure (P&P): Specialty Medication Administration Site of Care Policy: MHI Pharm 11
- ❒ If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare, if applicable.

COVERAGE EXCLUSIONS

All other uses of Provenge (Sipuleucel-T) that are not an FDA-approved indication AND not included in the 'Coverage Criteria' section of this policy are considered not medically necessary. This is subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

Repeat treatment in individuals who have received Provenge (Sipuleucel-T) previously is not supported by compendia and not considered not medically necessary.

BACKGROUND/SUMMARY

CLINICAL EFFICACY

- In a series of 3 phase III trials with almost identical design, sipuleucel-T was compared to placebo (consisting of peripheral blood mononuclear cells that were not activated ex vivo) in patients with asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer.
- The first 2 trials utilized time to progression of disease as the primary outcome (Studies 9901 and 9902A); neither showed a statistical difference between the treatment group and placebo. The third trial utilized overall survival as the primary outcome (Study 9902B, IMPACT).
- In the third trial, the median overall survival was statistically higher in the sipuleucel-T group with a hazard ratio for death of 0.78, a 22% relative risk reduction with an absolute increase of 4.2 months in overall survival. Similar to the first two trials, the third trial did not show a difference in time to progression of disease and did not show any disease response or stabilization.

The IMPACT Trial: Immunotherapy for Prostate AdenoCarcinoma Trial [Kantoff P, et al. IMPACT trial]
The primary sipuleucel-T study was a randomized, double-blind, placebo-controlled study enrolling 512 patients with asymptomatic or minimally symptomatic metastatic castration-resistant (hormone-refractory) prostate cancer

- Eligible patients had metastatic disease in the soft tissue and/or bone with evidence of progression at these sites or by serial PSA measurements and testosterone levels less than 50 ng/dL following medical or surgical castration.
- Patients with visceral (liver, lung, or brain) metastases, those with moderate to severe prostate cancer–related pain, or those using narcotics for cancer-related pain were excluded. Patients received sipuleucel-T (341 patients) or control (autologous peripheral blood mononuclear cells that had not been activated, 171 patients) and were stratified by primary Gleason score, number of bone metastases, and bisphosphonate use.
- The median age was 71 years and 90% of patients were white. Thirty-five percent had undergone radical prostatectomy, 54% had received local radiotherapy, 82% had received combination androgen blockade, and 18% had received prior chemotherapy. Forty-eight percent of patients were receiving bisphosphonates.
- All patients had a baseline testosterone level less than 50 ng/mL. Eighty-two percent of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 and 58% had a primary Gleason score of 4 or higher.
- Approximately half (48%) of the patients had bone-only disease, 44% had bone and soft tissue disease, and 7% had soft tissue–only disease; 43% had more than 10 bony metastases.

- Median survival was 25.8 months in the sipuleucel-T group and 21.7 months in the control group (hazard ratio [HR], 0.775; 95% confidence interval [CI], 0.614 to 0.979; *P* = 0.032).
- Results were consistent in multiple subgroups, including prognostic groups (HR for Halabi survival of 18 months or longer, 0.798; HR for survival less than 18 months, 0.731), as well as groups defined by bisphosphonate use, primary Gleason score, number of bone metastases, disease localization, or ECOG score. Survival probability at 36 months was 32.1% in the sipuleucel-T group and 23% in the placebo group. At 48 months, survival probability was 20.5% in the sipuleucel-T group and 16% in the placebo group. Time to objective disease progression was similar in the sipuleucel-T and placebo groups (HR, 0.951; *P* = 0.628). [Kantoff P, et al. IMPACT trial]

Higano and colleagues (2009) examined the safety and effectiveness of sipuleucel-T in 2 identically designed, randomized, double-blind, placebo-controlled trials (D9901 and D9902A) conducted in men with advanced prostate cancer.

- A total of 225 patients were randomized in D9901 or D9902A to sipuleucel-T (n=147) or placebo (n= 78), given as 3 intravenous infusions approximately 2 weeks apart.
- Patients were followed for survival until death or a pre-specified cut-off of 36 months after randomization. In the integrated analysis of D9901 and D9902A, patients randomized to sipuleucel-T demonstrated a 33% reduction in the risk of death (HR, 1.50; 95% CI, 1.10 to 2.05; p = 0.011; log-rank).
- The treatment effect remained strong after performing adjustments for imbalances in baseline prognostic factors, post-study treatment chemotherapy use, and non-prostate cancer- related deaths. Additional support for the activity of sipuleucel-T is provided by the correlation between a measure of the product's potency, CD54 up-regulation, and overall survival.
- The most common adverse events associated with treatment were asthenia, chills, dyspnea, headache, pyrexia, tremor, and vomiting. These events were primarily grade 1 and 2, with durations of 1 to 2 days. The authors concluded that the integrated results of D9901 and D9902A demonstrated a survival benefit for patients treated with sipuleucel-T compared with those treated with placebo.
- The generally modest toxicity profile, coupled with the survival benefit, suggests a favorable risk-benefit ratio for sipuleucel-T in patients with advanced prostate cancer.

⌘ Double-blind, placebo-controlled phase 3 study enrolled 127 patients with progressive androgen-independent metastatic prostate cancer. Eligible patients had 25% or more cancer cells staining positive for PAP, an interval of at least 6 months since prior chemotherapy, an ECOG performance status of 0 or 1, the absence of pulmonary and/or visceral disease, and the absence of disease-related pain. Castrate levels of testosterone were documented, and androgen deprivation was continued throughout the study. Median age was 71 to 73 years (range, 47 to 86 years of age) and 91% of patients were white. The median Gleason score was 7, with 41% of patients having a Gleason score of 8 or higher. Patients were randomized to receive sipuleucel-T (82 patients) or placebo (45 patients) every 2 weeks for a total of 3 doses. Placebo consisted of autologous peripheral blood mononuclear cells that had not been activated. The primary end point was the time to objective disease progression. The secondary end point was the time to onset of disease-related pain. Survival was monitored for 3 years following randomization per protocol. If disease progression occurred in subjects randomized to placebo, they became eligible to receive open-label sipuleucel-T using a salvage protocol. At the time of data analysis, 115 of 127 patients had experienced objective disease progression. In the intent-to-treat (ITT) population, time to disease progression was 11.7 weeks in the sipuleucel-T group and 10 weeks in the control group (*P* = 0.052; HR, 1.45; 95% CI, 0.99 to 2.11). Median overall survival was 25.9 months for

patients treated with sipuleucel-T compared with 21.4 months for those treated with placebo ($P = 0.01$; HR, 1.7; 95% CI, 1.13 to 2.56). At 36 months, 34% of patients treated with sipuleucel-T were alive compared with 11% of placebo-treated patients. In patients with a Gleason score of 7 or lower (typically indicating less aggressive disease), the median time to disease progression was 16.1 weeks with sipuleucel-T and 9.1 weeks with control ($P = 0.001$; HR, 2.23; 95% CI, 1.37 to 3.73). Patients with a Gleason score of 7 or lower treated with sipuleucel-T also had a higher probability of remaining free of cancer-related pain ($P = 0.016$; HR, 2.67; 95% CI, 1.16 to 6.13) and showed an interim survival advantage over controls (30.7 vs 22.3 months; $P = 0.047$; HR, 1.89; 95% CI, 1 to 3.58). In patients with a Gleason score of 8 or higher, there were no advantages observed with sipuleucel-T therapy compared with the control group. PA2024-specific T-cell response was 8-fold greater in the sipuleucel-T–treated patients compared with controls (16.9 vs 1.99, $P = 0.0004$), and 7-fold greater in sipuleucel-T–treated patients with Gleason scores of 7 or lower than in sipuleucel-T–treated patients with Gleason scores of 8 or higher (49.6 vs 7.26, $P = 0.0065$). [Schellhammer PF, et al. 2005; Small EJ, et al. 2005; Small EJ, et al. 2006]

- Phase 3 study enrolling 98 patients with asymptomatic metastatic androgen-independent prostate cancer with tumor progression following hormonal therapy and no cancer-related pain or visceral metastases. Patients were randomized to receive sipuleucel-T or placebo every 2 weeks for 3 doses. The primary study end point was time to objective disease progression. Study enrollment was terminated early when the previous study did not meet its primary efficacy objectives. Survival of enrolled subjects was monitored for 3 years after randomization. The time to objective disease progression did not differ between sipuleucel-T and placebo. The median survival time in the ITT population was 19 months for sipuleucel-T–treated patients and 15.7 months for placebo-treated patients ($P = 0.332$; HR, 1.27; 95% CI, 0.78 to 2.07). At 36 months after randomization, 32% of sipuleucel-T patients and 21% of placebo patients were still alive. A secondary analysis based on a Cox proportional hazards model, which adjusted for predictive baseline characteristics, revealed a survival advantage for sipuleucel-T ($P = 0.023$; HR, 1.91; 95% CI, 1.09 to 3.35). [Higano CS, et al. 2005]

  In an integrated analysis of the 2 preceding studies, patients treated with sipuleucel-T demonstrated a 33% reduction in the risk of death (HR, 1.5; 95% CI, 1.1 to 2.05; $P = 0.011$) [Higano CS, et al. 2009]. In an integrated analysis of the three phase 3 studies, sipuleucel-T reduced the risk of death from any cause by 26.5% (HR, 0.735; $P < 0.001$) and extended median overall survival by 3.9 months compared with placebo. Overall survival at 36 months was 33% in the sipuleucel-T group and 20% in the placebo group.

- Efficacy was not demonstrated in a randomized, double-blind, placebo-controlled study enrolling 176 patients with androgen-dependent prostate cancer (Beer TM, et al. 2007)

CLINICAL PRACTICE GUIDELINES

National Comprehensive Cancer Center (NCCN)
NCCN has published updates to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) and NCCN Drugs & Biologics Compendium (NCCN Compendium™) for Prostate Cancer.

- The NCCN Prostate Panel added sipuleucel-T as a category 1 treatment recommendation for first-line treatment of asymptomatic patients with castration-resistant prostate cancer, and a 2a recommendation for second-line treatment for minimally symptomatic patients.
- The NCCN guidelines (2018) state that sipuleucel-T is appropriate for patients with ECOG performance status 0-1. It is not recommended for patients with liver metastases or a life expectancy less than 6 months.
- Sipuleucel-T for Small Cell/Neuroendocrine Prostate Cancer: NCCN clinical practice guideline on "Prostate cancer" (Version 2.2019) states that sipuleucel-T has not been studied in patients with visceral metastases; sipuleucel-T is not recommended for patients with small cell / neuroendocrine prostate cancer.

American Urological Association (2018)
In their guideline for Castration-Resistant Prostate Cancer, the American Urological Association (2018) recommends the following in relation to sipuleucel-T:

- Guideline Statement 5: Clinicians should offer abiraterone plus prednisone, enzalutamide, docetaxel, or sipuleucel-T to patients with asymptomatic or minimally symptomatic mCRPC with good performance status and no prior docetaxel chemotherapy. (Standard; Evidence Level Grade A [abiraterone plus prednisone and enzalutamide] / B [docetaxel and sipuleucel-T])
- Guideline Statement 10. Clinicians should not offer treatment with either estramustine or sipuleucel-T to patients with symptomatic, mCRPC with good performance status and no prior docetaxel chemotherapy. (Recommendation; Evidence Level Grade C)
- Guideline Statement 15. Clinicians should not offer sipuleucel-T to patients with symptomatic, mCRPC with poor performance status and no prior docetaxel chemotherapy. (Recommendation; Evidence Level Grade C)

DEFINITIONS

ECOG (Eastern Cooperative Oncology Group) A scale used to assess how an individual's disease is progressing, determine how the disease affects the daily living abilities of the individual, and determine appropriate treatment and prognosis (Oken, 1982):

0= Fully active, able to carry on all pre-disease performance without restriction
1= Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2= Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3= Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4= Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5= Dead

Gleason score The standard approach for grading prostate cancer depends on a Gleason score, which is based on pathologic evaluation of a prostatectomy specimen and is commonly estimated from prostate biopsy tissue. Prostate cancer patterns are assigned a number from 1-5; the score is created by adding the most common pattern and the highest-grade patterns. A Gleason score of 6 is low grade, 7 is intermediate grade, and a score of 8 to 10 is high grade cancer.

In 2014, the World Health Organization reorganized the Gleason score with the simpler ISUP (International Society of Urological Pathology) Grade Group system ranging from 1 (low) to 5 (very high). Many hospitals report both the Gleason score and the ISUP grade group, but there may be hospitals that still only report the old Gleason system.

ISUP Grade Group and Gleason Score Comparison

Risk Group	ISUP Grade Group	Gleason Score
Low	Grade Group 1	Gleason Score ≤ 6
Intermediate Favorable	Grade Group 2	Gleason Score 7 (3 + 4)
Intermediate Unfavorable	Grade Group 3	Gleason Score 7 (4 + 3)
High	Grade Group 4	Gleason Score 8
High	Grade Group 5	Gleason Score 9-10

APPENDIX

APPENDIX 1: Therapies for castration-resistant prostate cancer (CRPC)

Table 1 (below) from 2019 UpToDate, Inc. and/or its affiliates

Citation: Kantoff, PW. Immunotherapy for castration-resistant prostate cancer. Vogelzang, N (ed.) In: UpToDate Online. Jun 2019. Accessed: July 2019

Therapy	Indications	Route, Dose	Concomitant Steroids	Symptoms, disease burden	Contraindications	PSA response to treatment	Median overall survival benefit for men with metastatic disease*
Abiraterone	Metastatic CRPC	Oral, daily	Required	–	Severe liver dysfunction; hypokalemia; heart failure	Yes	Post docetaxel: 4.6 months[1] Chemotherapy naïve: 4.4 months[2]
Enzalutamide	Metastatic CRPC	Oral, daily	Not required	–	Seizures	Yes	4.8 months[3]
Enzalutamide	Nonmetastatic CRPC	Oral, daily	not required	–	Seizures	Yes	Metastasis-free survival: 36.6 versus 14.7 months[4]
Apalutamide	Nonmetastatic CRPC	Oral, daily	Not required	–	–	Yes	Metastasis-free survival: 40.5

							versus 16.2 months[5]
Sipuleucel-T	Pre or post docetaxel	IV, every 2 weeks for 3 doses	Possibly contraindicated	Asymptomatic or minimally symptomatic	Steroids; narcotics for cancer-related pain; GM-CSF; liver metastases	No	4.1 months[6]
Docetaxel	Metastatic CRPC¶	IV, every 3 weeks	Required	–	Moderate liver dysfunction; cytopenias	Yes	2.5 months[7]
Cabazitaxel	Post docetaxel	IV, every 3 weeks	Required	–	Moderate liver dysfunction; cytopenias	Yes	2.4 months[8]
Radium-223	Symptomatic bone metastases with no known visceral metastases	IV, every 4 weeks	Not required	Symptomatic bone metastases	Visceral metastases	Not reported	3.6 months[9]

PSA: prostate-specific antigen; IV: intravenously; GM-CSF: granulocyte-macrophage colony-stimulating factor. *The therapeutic approaches have not been compared with each other in large randomized trials. Only enzalutamide and apalutamide have been evaluated in men whose only evidence of disseminated disease is an elevated or rising serum PSA. ¶ Docetaxel is also indicated for castration-sensitive disease in combination with androgen deprivation therapy for metastatic prostate cancer.

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CODING INFORMATION: THE CODES LISTED IN THIS CLINICAL POLICY ARE FOR INFORMATIONAL PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE AND INCLUSION OR EXCLUSION OF ANY CODES DOES NOT GUARANTEE COVERAGE. PROVIDERS SHOULD REFERENCE THE MOST UP-TO-DATE SOURCES OF PROFESSIONAL CODING GUIDANCE PRIOR TO THE SUBMISSION OF CLAIMS FOR REIMBURSEMENT OF COVERED SERVICES.

CPT	Description

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

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Policy History	Approval
Policy Developed Peer Review: AMR Peer Review Network. 6/7/2019. Practicing Physician. Board certified in oncologist or a urologist	10/26/2011
Revision* Peer Review: AMR Peer Review Network. 7/16/2019. Practicing Physician. Board certified in urology Policy retired in 2017 and converted to PA criteria 'Standard Oncology Criteria.' Provenge reviewed and developed as an MCP for P&T in Q3 2019.	P&T Q3 2019
Annual Review* No coverage criteria changes with this annual review. Minor revisions, including clarification and addition of language, however no change to intent.	P&T Q3 2020

*NOTE: All content, clinical evidence, coverage criteria, practice guidelines, appendices and reference sections were reviewed and revised with the most recent medical literature and available evidence for both 'Annual Reviews' and 'Revisions.' Revisions include notable content updates or revisions that which may have affected criteria or requires review by a practicing specialist, Peer Reviewer. The revisions noted below but may not be all-inclusive of all revised criteria and content in each policy; refer to MCP for all revisions and complete context.