Prostate Cancer Vaccine - Provenge AHM

Clinical Indications

- Sipuleucel-T (Provenge) is considered medically necessary for the treatment of adults with metastatic castrate-resistant prostate cancer who are asymptomatic or minimally symptomatic with Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, and who have no liver metastases and a life expectancy of greater than 6 months
- Sipuleucel-T (Provenge) is considered medically necessary for members who meet **ALL** of the following criteria:
  - Adult men (18 years of age or older) with histologically confirmed adenocarcinoma of the prostate with radiologic evidence of metastases to soft tissue, lymph nodes or bone
  - Treatment with surgical (bilateral orchiectomy) castration or three or more months of chemical castration (luteinizing hormone releasing hormone (LHRH) agonists or antagonists[^A]); for members treated with chemical castration, serum testosterone must have been less than 50 ng/dL at initiation of chemical castration to document adequacy of castration
  - 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
    - 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: An increase in PSA over a previous reference value, where the PSA value is a measured a minimum of one week from the reference value, and the PSA measurement is a minimum of 25 percent greater than the reference value, and an absolute-value increase in PSA of at least 5 ng/ml over the reference value, and this PSA increase is confirmed by a second value;
• Member is asymptomatic or minimally symptomatic, without cancer-related bone pain or use of opioid analgesics for cancer pain
• Member has Eastern Cooperative Oncology Group (ECOG) \[^B\] performance status of 0 or 1;
• Member has no visceral (liver, lung or brain) metastases
• Member has expected survival of at least 6 months

- Current role remains uncertain. Based on review of existing evidence, there are currently no clinical indications for this technology. See Inappropriate Uses for more detailed analysis of the evidence base. Sipuleucel-T investigational for other indications (e.g., prevention of prostate cancer and treatment of localized prostate cancer, glioblastoma, and sarcoma; not an all-inclusive list) because its effectiveness for these indications has not been established.

- Dosing Information: According to the FDA-approved labeling of Provenge, the recommended course of therapy for sipuleucel-T is 3 complete doses, given at approximately 2-week intervals. 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. Administration of more than 3 complete doses of sipuleucel-T is considered experimental and investigational.

### Evidence Summary

#### Background

- Prostate cancer, accounting for 33% of all male cancers worldwide, is the second leading cause of cancer death in men, exceeded only by lung cancer. The disease is histologically evident in as many as 34% of men during their fifth decade of life and in up to 70% of men aged 80 years old and older. In the United States, prostate cancer represents the most common cancer among men, with an estimated 192,280 new cases diagnosed in 2009. The median survival for men with metastatic castrate-resistant prostate cancer is 1 to 2 years, with improvements in survival seen primarily with cytotoxic chemotherapy (docetaxel-based therapies). In the field of metastatic castration-resistant prostate cancer, systemic therapy options are limited and survival benefit remains to be seen with the new therapies. Staging of prostate cancer entails the size of the tumor, if lymph nodes are affected, if the tumor has metastasized, and the appropriate course of treatment. Circulating tumor cells may provide prognostic information and will likely become an important aspect of future clinical decision-making (Lassi and Dawson, 2010).

- Standard systemic treatment of prostate cancer today is comprised of anti-hormonal and cytostatic agents. Vaccine therapy of prostate cancer is attractive because of the presence of tumor-associated antigens such as prostate-specific antigen (PSA), prostatic acid phosphatase (PAP), prostate-specific membrane antigen, and others. Most prostate cancer vaccine trials have demonstrated some activation of the immune system, limited clinical
success, and few adverse effects. One strategy to overcome the problem of limited clinical success of vaccine therapies in prostate cancer could be strict patient selection. The clinical course of patients with prostate cancer (even in those with PSA relapse following surgery or radiotherapy with curative intention, or those with metastatic disease) can vary significantly. In patients with organ-confined prostate cancer, the most promising immunotherapeutic approach would be an adjuvant therapy following surgery or radiotherapy. Patients with PSA relapse following surgery or radiotherapy could also benefit from immunotherapy because tumor burden is usually low. However, most patients in prostate cancer vaccine trials had metastatic hormone-refractory prostate cancer (HRPC). High tumor burden correlates with immune escape phenomena. Nevertheless, 2 years ago, it was reported, for the first time, that a tumor vaccine can prolong survival compared with placebo in patients with HRPC. This was demonstrated with the vaccine sipuleucel-T (APC-8015; Provenge), a mixture of cells obtained from the patient's peripheral blood by leukapheresis followed by density centrifugation and exposition. The biologics license application for this vaccine was denied by the U.S. Food and Drug Administration (FDA) in mid-2007, however, because the trial had failed to reach the primary endpoint (prolongation of time to tumor progression). Another interesting approach is a vaccine made from whole tumor cells: GVAX. This vaccine is presently being studied in phase III trials against, and in combination with, docetaxel. The results from these trials will become available in the near future. Besides the precise definition of the disease status of patients with prostate cancer, combinations of vaccine therapy with radiotherapy, chemotherapy, and/or hormonal therapy are approaches that look promising and deserve further investigation (Doehn, et al., 2008).

- Sipuleucel-T is an immunotherapeutic cellular product, which includes autologous dendritic cells pulsed ex vivo with a recombinant fusion protein (PA2024) consisting of granulocyte macrophage colony-stimulating factor and PAP. It is designed to stimulate the patient's T-cells to recognize and attack prostate cancer cells that express PAP antigen (Harzstark and Small, 2008).

- In a phase III clinical trial, Small and colleagues (2006) evaluated the safety and effectiveness of sipuleucel-T in patients with metastatic, asymptomatic HRPC. A total of 127 patients were randomly assigned in a 2:1 ratio to receive 3 infusions of sipuleucel-T (n = 82) or placebo (n = 45) every 2 weeks. On disease progression, placebo patients could receive APC8015F, a product made with frozen leukapheresis cells. Of the 127 patients, 115 patients had progressive disease at the time of data analysis, and all patients were followed for survival for 36 months. The median for time to disease progression (TTP) for sipuleucel-T was 11.7 weeks compared with 10.0 weeks for placebo (p = 0.052, log-rank; hazard ratio [HR], 1.45; 95% confidence interval [CI], 0.99 to 2.11). Median survival was 25.9 months for sipuleucel-T and 21.4 months for placebo (p = 0.01, log-rank; HR, 1.70; 95% CI, 1.13 to 2.56). Treatment remained a strong independent predictor of overall survival after adjusting for prognostic factors using a Cox multi-variable regression model (p = 0.002, Wald test; HR, 2.12; 95% CI, 1.31 to 3.44). The median ratio of T-cell stimulation at 8 weeks to pre-treatment was 8-fold higher in sipuleucel-T-treated patients (16.9 versus 1.99; p < 0.001). Sipuleucel-T therapy was well-tolerated. The authors concluded that while the improvement in the primary end
point of TTP did not achieve statistical significance, this study suggested that sipuleucel-T may provide a survival advantage to asymptomatic HRPC patients.

- Patel and Kockler (2008) reviewed the design, efficacy, safety, dosing, therapeutic, and pharmaco-economic considerations of sipuleucel-T. English-language literature searches of Medline (1966 to September 2007) and the Cochrane Database (2007, Issue 3) were performed using the terms sipuleucel-T, APC8015, and prostate cancer vaccine. Other data sources were identified from bibliographies of selected articles and from press releases. All published articles or abstracts on human studies of sipuleucel-T for androgen-independent prostate cancer (AIPC) were reviewed for inclusion. Manufacturer Web sites, FDA documents, and the clinical trials registry were used to obtain information regarding ongoing clinical trials. Androgen-independent prostate cancer is an incurable disease with a median survival rate of 18 to 20 months. Docetaxel-based chemotherapy is currently the only FDA-approved treatment for AIPC with a survival benefit (2.4 months). Sipuleucel-T is a novel active cellular immunotherapy under investigation for the treatment of metastatic, asymptomatic AIPC. In clinical trials, the primary endpoint of TTP was not met; however, an under-powered analysis of data suggests that sipuleucel-T prolongs survival by a median of 4.5 months compared with placebo. Sipuleucel-T has been relatively well-tolerated, although a possible increased risk of cerebrovascular events may exist. In May 2007, the FDA did not approve the biologics license application for sipuleucel-T since the primary endpoint of the phase III trials was not met. The authors concluded that metastatic AIPC is an incurable disease that currently has limited treatment options. If improved survival is shown, sipuleucel-T may become the first approved active cellular immunotherapy for treating metastatic, asymptomatic AIPC.

- 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.
• Drake and Antonarakis (2010) stated that prostate cancer is the second most common cause of cancer-related death among men in the United States. Along with initial therapy using surgery, radiotherapy, or cryotherapy, hormonal therapy is the mainstay of treatment. For men with metastatic disease, docetaxel-based chemotherapy is FDA-approved, and provides a significant survival advantage. This relative paucity of treatment options drives an ongoing quest for additional treatment modalities; among these is immunotherapy. The concept that prostate cancer is a malignancy that can be targeted by the immune system may seem counter-intuitive; certainly kidney cancer and melanoma are more traditionally thought of as immune responsive cancers. However, prostate cancer arises in a relatively unique organ and may express a number of antigens against which an immune response can be generated. More importantly, several of these agents have now demonstrated a significant survival benefit in randomized controlled clinical trials.

• On April 29, 2010, the FDA approved Provenge (sipuleucel-T, Dendreon Corporation, Seattle, WA) for the treatment of asymptomatic or minimally symptomatic prostate cancer that has metastasized and is resistant to standard hormone treatment. The effectiveness of Provenge was studied in a randomized, double-blind, placebo-controlled, multi-center trial in patients with asymptomatic or minimally symptomatic metastatic HRPC. Eligible patients had metastatic disease in the soft tissue and/or bone with evidence of progression either at these sites or by serial PSA measurements. Exclusion criteria included visceral (liver, lung, or brain) metastases, moderate-to-severe prostate cancer-related pain, and use of narcotics for cancer-related pain. A total of 512 patients were randomized in a 2:1 ratio to receive Provenge (n = 341) or control (n = 171). The median age was 71 years, and 90% of the patients were Caucasian; 35% of patients had undergone radical prostatectomy, 54% had received local radiotherapy, and 82% had received combined androgen blockade. All patients had baseline testosterone levels less than 50 ng/ml; 48% of patients were receiving bisphosphonates and 18% had received prior chemotherapy, including docetaxel. A total of 82% of patients had an Eastern Cooperative Oncology Group performance status of 0; 58% had primary Gleason scores of 4 or more; 44% had bone and soft tissue disease; 48% had bone-only disease; 7% had soft tissue-only disease; and 43% had greater than 10 bony metastases. Patients treated with Provenge showed an increase in overall survival of 4.1 months. The median survival for patients receiving Provenge treatments was 25.8 months, as compared to 21.7 months for those who did not receive the treatment. Overall, Provenge reduced the risk of death by 22.5% compared to the control group (HR = 0.775).

• The NCCN Prostate Panel added sipuleucel-T as a category 1 treatment recommendation for patients with castration-recurrent prostate cancer. The NCCN guidelines state that sipuleucel-T is appropriate for asymptomatic or minimally symptomatic patients with ECOG performance status 0-1. It is not recommended for patients with visceral disease and a life expectancy less than 6 months.

• Provenge is administered intravenously in a 3-dose schedule administered at about 2-week intervals (range of 1 to 15 weeks). It is administered over a period of about 60 minutes. Almost all of the patients who received Provenge had some type of adverse reaction. Common adverse reactions included back pain, chills, fatigue, fever, headache,
joint ache, and nausea. The majority of adverse reactions were mild or moderate in severity. Serious adverse reactions, reported in about 25% of the patients receiving Provenge, included some acute infusion reactions and stroke. Cerebrovascular events, including hemorrhagic and ischemic strokes, were observed in 3.5% of patients in the Provenge group compared with 2.6% of patients in the control group.

- Combination immunotherapy with Provenge plus other agents has been studied in patients with prostate cancer. Rini and colleagues (2006) noted that bevacizumab is a recombinant antibody against vascular endothelial growth factor, a pro-angiogenic protein with inhibitory effects on antigen-presenting cells (APC). These researchers carried out a clinical trial to determine the PSA and immunomodulatory effects of combination immunotherapy with sipuleucel-T plus bevacizumab in patients with serologic progression of prostate cancer after definitive local therapy. Patients with androgen-dependent prostate cancer who had received prior definitive therapy with non-metastatic, recurrent disease as manifested by a rising PSA of between 0.4 ng/ml and 6.0 ng/ml were enrolled. Sipuleucel-T was given intravenously (i.v.) on weeks 0, 2, and 4. Bevacizumab was given at a dose of 10 mg/kg i.v. on weeks 0, 2, 4, and every 2 weeks thereafter until toxicity or disease progression. Changes in PSA were recorded and the PSA doubling time (PSADT) was calculated. Immune response versus PA2024 was measured at baseline and after treatment by T-cell proliferation and interferon-gamma enzyme-linked immunospot (ELISPOT) assays. A total of 22 patients were treated. One patient achieved a greater than or equal to 50% decrease in PSA; 9 patients exhibited some decrease in PSA from baseline, ranging from 6% to 72%, with the PSA of 3 patients decreasing at least 25%. The median pre-treatment PSADT for the 20 evaluable patients was 6.9 months and the median post-treatment PSADT was 12.7 months (p = 0.01). All patients demonstrated induction of an immune response against PA2024. The authors concluded that the combination of sipuleucel-T and bevacizumab induces an immune response and modulates PSA in patients with biochemically recurrent prostate cancer.

- Antonarakis and Drake (2010) stated that an emerging paradigm for the treatment of prostate cancer focuses on using immunotherapy plus check-point antagonists or in combination with conventional therapies in patients with early-stage disease. Such approaches are likely to yield optimal results, but must carefully be explored in well-designed phase II studies.

- Lubaroff (2012) presented important information about the current state of the art for vaccine immunotherapy of prostate cancer. It included important preclinical research for each of the important prostate cancer vaccines to have reached clinical trials. To-date, the only prostate cancer vaccine that has completed phase III trials and has been approved and licensed by the FDA is Sipuleucel-T, which immunizes patients against the prostate-associated antigen PAP. A phase III trial is currently underway using the vaccinia-based PSA vaccine Prostvac-TRICOM. Other immunotherapeutic vaccines in trials include the Ad/PSA vaccine Ad5-PSA and the DNA/PAP vaccine. A cellular vaccine, GVAX, has been in clinical trials, but has not seen continuous study.

- Amato and Stepankiw (2012) reviewed the development of the combination of modified vaccinia Ankara (MVA) to deliver the tumor-associated antigen 5T4 as a novel
immunotherapeutic vaccine. The onco-fetal antigen 5T4 is highly expressed in 80% of breast, kidney, colorectal, prostate and ovarian carcinomas, making it an ideal antigen for vaccine therapy. To-date, more than 3,000 doses of MVA-5T4 have been administered to patients with colorectal, renal and prostate cancer, with rare occurrences of grade 3 or 4 vaccination-related adverse events being observed. Studies have demonstrated that MVA-5T4 is safe and highly immunogenic, both as monotherapy and in combination with other standard of care therapies. Although an immune response has been observed, anti-tumor activity has been modest or absent in clinical trials.

- A phase III trial resulted in the development of an immune response surrogate that is to be applied to all future MVA-5T4 clinical trials. The authors concluded that with minimal side effects and the ability to produce a strong immunogenic response, MVA-5T4 is a viable addition to the cancer therapy arsenal.

- Reardon et al (2013) stated that outcome for glioblastoma (GBM) remains poor. The overall survival benefit recently achieved with immunotherapeutics -- ipilimumab for melanoma and sipuleucel-T for prostate cancer -- support evaluation of immunotherapies for other challenging cancers, including GBM. Much historical dogma depicting the central nervous system (CNS) as immune-privileged has been replaced by data demonstrating CNS immune-competence and active interaction with the peripheral immune system. Several glioma antigens have been identified for potential immunotherapeutic exploitation. Active immunotherapy studies for GBM, supported by pre-clinical data, have focused on tumor lysate and synthetic antigen vaccination strategies.

- Results to-date confirmed consistent safety, including a lack of autoimmune reactivity; however, modest efficacy and variable immunogenicity have been observed. The authors concluded that these findings underscored the need to optimize vaccination variables and to address challenges posed by systemic and local immunosuppression inherent to GBM tumors. Moreover, they noted that additional immunotherapy strategies are also in development for GBM; future studies may consider combinatorial immunotherapy strategies with complimentary actions.

- Goldberg (2013) stated that although molecularly targeted inhibitors are of great interest in treating sarcoma patients, immunotherapy is emerging as a plausible therapeutic modality because of the recent advances in other cancer types that may be translated to sarcoma. The licensing of ipilimumab for melanoma and sipuleucel-T for prostate cancer, and the remarkable success of immunotherapy for some childhood cancers, suggest a role for immunotherapy in the treatment of tumors like sarcoma. The author described the current advances in immunotherapy and how they can be applied to sarcoma, and discussed the recent literature and selected clinical trials. Evidence supporting treatment with immunotherapy alone in sarcoma as well as potential incorporation of immunotherapy into treatment for sarcoma was reviewed.

- The author concluded that sarcoma is a disease for which new treatments are needed. Immunotherapies have different mechanisms of action from most current therapies and could work in concert with them. Recent advances in sarcoma biology and cancer immunotherapy suggest that the understanding of the immune system has reached the
point where it can be used to augment both targeted and multi-modality therapy for sarcoma.

References

- Dendreon Corporation. Provenge (sipuleucel-T) suspension for intravenous infusion. Prescribing Information. Seattle, WA: Dendreon Corporation; 2010. Available at:

- National Horizon Scanning Centre (NHSC). Sipuleucel-T (Provenge) for metastatic castration resistant prostate cancer - first line. Horizon Scanning Review. Birmingham, UK: National Horizon Scanning Centre (NHSC); April 1, 2011

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Footnotes

[A] LHRH agonists (analogs) include leuprolide (Lupron, Viadur, Eligard), goserelin (Zoladex), triptorelin (Trelstar), and histrelin (Vantas). Degarelix (Firmagon) is an LHRH antagonist that is thought to work like LHRH agonists. See CPB 501, Gonadotropin-Releasing Hormone Analogos and Antagonists [ A in Context Link 1 ]

[B] OEG- Grade 0 - Fully active, able to carry on all pre-disease performance without restriction. Grade 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. Grade 2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours. Grade 3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours. Grade 4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair Grade 5 - Dead [ B in Context Link 1 ]

Codes

CPT® or HCPCS: 96401, 96402, 96405, 96406, 96409, 96411, 96413, 96415, 96416, 96417, Q2043