Proposed Decision Memo for Autologous Cellular Immunotherapy Treatment of Metastatic Prostate Cancer (CAG-00422N)

Decision Summary

The Centers for Medicare and Medicaid Services (CMS) proposes that the evidence is adequate to conclude that the use of autologous cellular immunotherapy treatment - sipuleucel-T; PROVENGE® improves health outcomes for Medicare beneficiaries with asymptomatic or minimally symptomatic metastatic castrate-resistant (hormone refractory) prostate cancer, and thus is reasonable and necessary for that indication under 1862(a)(1)(A) of the Social Security Act (the Act).

We are requesting public comments on this proposed determination pursuant to section 1862 (l) of the Act. After considering the public comments, we will make a final determination and issue a final decision memorandum.

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Proposed Decision Memo

TO: Administrative File CAG-00422N

FROM:

Louis B. Jacques, MD
Director, Coverage and Analysis Group

Tamara Syrek Jensen, JD
Deputy Director, Coverage and Analysis Group

James Rollins, MD, MSHA, PhD.
Director, Division of Items and Devices

Leslye K. Fitterman, Ph.D.
Lead Analyst and Epidemiologist, Division of Items and Devices

Lori Paserchia, MD
Medical Officer, Division of Medical and Surgical Services

Eileen Pencek, RN, BSN, MBA
Analyst, Division of Medical and Surgical Services

SUBJECT: Internal Request for Autologous Cellular Immunotherapy Treatment of Metastatic Prostate Cancer

DATE: March 30, 2011

I. Proposed Decision

The Centers for Medicare and Medicaid Services (CMS) proposes that the evidence is adequate to conclude that the use of autologous cellular immunotherapy treatment - sipuleucel-T; PROVENGE® improves health outcomes for Medicare beneficiaries with asymptomatic or minimally symptomatic metastatic castrate-resistant (hormone refractory) prostate cancer, and thus is reasonable and necessary for that indication under 1862(a)(1)(A) of the Social Security Act (the Act).

We are requesting public comments on this proposed determination pursuant to section 1862 (l) of the Act. After considering the public comments, we will make a final determination and issue a final decision memorandum.

II. Background Information

Prostate cancer

Prostate cancer is the most common non-cutaneous cancer in men in the United States (Jemal, 2009). In 2009 an estimated 192,280 new cases of prostate cancer were diagnosed and an estimated 27,360 deaths were reported. The National Cancer Institute (NCI) states that prostate cancer is predominantly a cancer of older men; the median age at diagnosis is 72 years. "More than 2 million men in the U.S. who have been diagnosed with prostate cancer at some point are still alive today" (Mark, 2010).

The TNM classification is used to define the extent of the cancer where "T" stands for primary tumor; "N" stands for regional lymph nodes; and "M" stands for distant metastasis. The extent of the tumor is generally determined using a number of techniques including digital rectal examination, a surgical procedure/biopsy and imaging studies such as CT, ultrasound, radionuclide bone scan and perhaps magnetic resonance imaging (MRI). The location of the primary tumor can range from confined within the prostate gland to extension beyond the wall of the prostate gland to adjacent structures to spread throughout the body. The extent of regional nodal involvement as well as distant metastasis is stated as present or absent. To further characterize the tumor, the Gleason score, determined upon microscopic examination of a tissue sample, is used to report the histopathologic grade of the tumor. Based on the TNM designations as well as Gleason score, one of four stages of prostate cancer is declared.

The TNM-based stage is used in clinical practice to determine the prognosis. The NCI (NCI Prostate cancer treatment [PDQ®]) notes that the "extent of the tumor is related to survival for patients with prostate cancer. When the cancer is confined to the prostate gland, median survival in excess of five years can be anticipated. Patients with locally advanced [i.e., the cancer is no longer confined to the prostate gland but has not spread to distant parts of the body] cancer are not usually curable, and a substantial fraction will eventually die of the tumor, though median survival may be as long as five years. If prostate cancer has spread to distant organs, current therapy will not cure it. Median survival is usually one to three years, and most such patients will die of prostate cancer. Even in this group of patients, however, indolent clinical courses lasting for many years may be observed." Patient's age, the serum PSA level and comorbidities can also impact the prognosis.

The TNM-based stage as well as the serum prostate specific antigen (PSA) level are also used in clinical practice to guide treatment and estimate the risk of recurrence after treatment. Hence, treatment recommendations will vary considerably; potential therapies include surgery, anticancer chemotherapy, radiation therapy and/or androgen deprivation therapy. Active surveillance (a.k.a., watchful waiting) may also play a role depending on the clinical circumstances and patient preference. As noted by Mark, et al., "After initial treatment, patients are monitored for recurrence by measuring PSA levels on a regular basis and imaging tests, if a distant metastasis is clinically suspected. If cancer recurs, and imaging workup indicates the presence or high suspicion of metastasis, androgen-deprivation therapy (ADT) is the standard therapy. ADT in the form of various medications or bilateral orchiectomy are equally effective. Effective ADT will produce a decrease in serum PSA levels, pain relief, and regression of soft tissue metastases. However, ADT does not permanently suppress the progression of cancer, and eventually most patients will experience a rise in PSA levels, followed by development and/or progression of metastases. Such a state of advanced cancer is called castrate-resistant, metastatic prostate cancer." This clinical state is also referred to as castration-resistant, metastatic prostate cancer.

Once the patient has castration-resistant, metastatic prostate cancer, further treatment consists of some combination of anticancer chemotherapy with docetaxel and steroids, mitoxantrone and steroids, secondary ADT, palliative radiotherapy or radionucleide therapy and bisphosphonates (NCCN, 2010). Additional subsequent therapies according to the 2010 NCCN guideline include best supportive care, enrollment in a clinical trial and salvage chemotherapy with mitoxantrone and steroids or with cabazitaxel and steroids. Despite these treatments, the median survival for patients with castration-resistant, metastatic prostate cancer is generally less than two years (Mark, 2010).

As of the date of this proposed decision memorandum (PDM), docetaxel and cabazitaxel (Jevtana®) are the only anticancer treatments that have demonstrated a prolongation of survival in randomized clinical trials for patients with castration-resistant prostate cancer. The median survival for patients with castration-resistant, metastatic prostate cancer who received docetaxel was 18.9 months compared to 16.5 months in patients who received mitoxantrone in a Phase 3 randomized trial that served as the basis for Food and Drug Administration (FDA) approval (FDA SBRA document). The patients in the docetaxel arm of that trial also had a greater relief in pain and a greater increase in quality of life measurements compared to patients in the mitoxantrone arm (Mark, 2010). It should be noted that mitoxantrone has shown in clinical studies to have a palliative effect in patients with prostate cancer but not an effect on survival. The most common (frequency ≥30%) adverse events associated with docetaxel were hair loss, nausea and vomiting, fatigue, sensory neuropathy, and neutropenia (Mark, 2010).

Cabazitaxel, which received FDA approval in June of 2010, is indicated for use in combination with prednisone for the treatment of patients with castration-resistant, metastatic prostate cancer who were previously treated with a docetaxel-containing regimen. In the randomized, open-label clinical trial the median survival was 15.1 months for patients who received cabazitaxel and 12.7 months for patients who received mitoxantrone. The most common (frequency ≥10%) adverse events in the cabazitaxel arm included neutropenia, anemia, thrombocytopenia, diarrhea, nausea, vomiting, hematuria, peripheral neuropathy and dyspnea (U.S. Food and Drug Administration; June 18, 2010).

Autologous Cellular Immunotherapy

In 2010 the FDA approved sipuleucel-T (Provenge®; APC8015), for patients with castration-resistant, metastatic prostate cancer. The posited mechanism of action, immunotherapy, is different from that of anticancer chemotherapy such as docetaxel. This is the first immunotherapy for prostate cancer to receive FDA approval.

The goal of immunotherapy is to stimulate the body's natural defenses (such as the white blood cells called dendritic cells, T-lymphocytes and mononuclear cells) in a specific manner so that they attack and destroy, or at least prevent the proliferation of, cancer cells. Specificity is attained by intentionally exposing a patient's white blood cells to a particular protein (called an antigen) associated with the prostate cancer. This exposure "trains" the white blood cells to target and attack the prostate cancer cells. Clinically this is expected to result in a decrease in the size and/or number of cancer sites, an increase in the time to cancer progression, and/or an increase in survival of the patient.

For the benefit of the lay reader, sipuleucel-T differs from other infused anti-cancer therapies. Most such anti-cancer therapies are manufactured and sold by a biopharmaceutical company and then purchased by and dispensed from a pharmacy. In contrast, once the decision is made to treat with sipuleucel-T, a multi-step process is used to produce sipuleucel-T. Sipuleucel-T is made individually for each patient with his own white blood cells. The patient’s white blood cells are removed via a procedure called leukapheresis. In a laboratory the white blood cells are exposed to PA2024, which is a molecule created by linking prostatic acid phosphatase (PAP) with granulocyte/macrophage-colony stimulating factor (GM-CSF). PAP is an antigen specifically associated with prostate cancer cells; GM-CSF is a protein that targets a receptor on the surface of white blood cells. Hence, PAP serves to externally manipulate the immunological functioning of the patient's white blood cells while GM-CSF serves to stimulate the white blood cells into action. As noted in the FDA's clinical review, each dose of sipuleucel-T contains a minimum of 40 million treated white blood cells, however there is "high inherent variability" in yield of sipuleucel-T from leukapheresis to leukapheresis in the same patient as well as from patient to patient. The treated white blood cells are then infused back into the same patient. The FDA-approved dosing regimen is three doses with each dose administered two weeks apart. The total treatment period is four weeks.

III. History of Medicare Coverage

Medicare has no current National Coverage Determination (NCD) for autologous cellular immunotherapy treatment - sipuleucel-T; PROVENGE®. Local Medicare contractors have discretion to determine coverage in the absence of an NCD.

A. Current Consideration

CMS opened this PDM to determine whether or not autologous cellular immunotherapy is reasonable and necessary under sections 1862(a)(1)(A) and/or 1862(a)(1)(E) of the Act.

B. Benefit Category

Medicare is a defined benefit program. An item or service must fall within a benefit category as a prerequisite to Medicare coverage is that an item or services must meet one of the statutorily defined benefit categories in the Social Security Act and not otherwise be excluded.

PROVENGE®(sipuleucel-T) falls within medical and other health services §1861(s)(2)(A) and §1861(s)(2)(B) of the Act as services and supplies furnished as incident to a physician's services commonly furnished in a physician's office and as services and supplies commonly furnished as incident to a physician's services during a hospital outpatient/clinic visit respectively

IV. Timeline of Recent Activities

June 30, 2010 – Tracking sheet posted on CMS website.

July 30, 2010 – End of comment period on the tracking sheet

November 17, 2010 – MEDCAC Meeting

March 30, 2011 – Proposed decision memorandum posted on the CMS website

V. FDA Status

In 2010 PROVENGE® (sipuleucel-T) Suspension for Intravenous Infusion received U.S. FDA approval for one indication and usage. As stated in the label, "PROVENGE is an autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer."

VI. General Methodological Principles

When making NCDs under §1862(a)(1)(A), CMS generally evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for beneficiaries. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that the Agency normally utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix A.

Public commenters sometimes cite the published clinical evidence and provide CMS with useful information. Public comments that provide information based on unpublished evidence, such as the results of individual practitioners or patients, are less rigorous and, therefore, less useful for making a coverage determination. CMS uses the initial comment period to inform the public of its proposed decision. CMS responds in detail to the public comments that were received in response to the proposed decision when it issues the final decision memorandum.

VII. Evidence

A. Introduction

This PDM organizes the evidence according to FDA status: labeled indication (a.k.a, on label) or off label indications. Only evidence from Phase 3 studies published as full-text, peer-reviewed literature articles was assessed. Unlike Phase 1 and Phase 2 trial designs, Phase 3 trial designs by nature incorporate methods such as randomization, control and blinding to minimize the potential for bias and confounding that can negatively impact the internal validity of a study. Appendix A presents more information regarding methodological considerations. Furthermore, Phase 3 studies in general focus on an endpoint that addresses clinical utility such as survival (as opposed to a surrogate endpoint or a biomarker), which is consistent with CMS' focus on health outcomes. Lastly, Phase 3 studies generally have larger sample sizes, which permit a robust analysis of the primary efficacy endpoint as well as the safety profile.

Health outcomes of interest to CMS for patients with prostate cancer include survival, disease progression and quality of life. CMS prefers to use a holistic approach to assessing the benefit of a medical product for Medicare patients. For example, while a delay in tumor progression may be considered by some to be a good intermediate or surrogate outcome, a coincident onset or increase of toxicity due to treatment may contradict the usefulness of tumor progression as a predictor of improved overall survival or improved quality of life. Under such a circumstance, an alternative management program may be a better strategy for the patient with prostate cancer.

B. Discussion of Evidence Reviewed

1. Questions:

The development of an assessment in support of Medicare coverage decisions under §1862(a)(1)(A) is based on the same general question for most PDMs: "Is the evidence sufficient to conclude that the application of the item or service under study will improve health outcomes for Medicare patients?" For this PDM, the questions of interest are:

a.

Is the evidence sufficient to conclude that autologous cellular immunotherapy treatment of metastatic prostate cancer in men whose disease is castration-resistant and who are asymptomatic or minimally symptomatic improves health outcomes of Medicare beneficiaries?

b.

Is the evidence sufficient to conclude that autologous cellular immunotherapy treatment of prostate cancer in men that is not metastatic and/or whose disease is not castration-resistant and/or who are more than minimally symptomatic improves health outcomes of Medicare beneficiaries?

2. External Technology Assessments (TA)

An Internet-based search of the Cochrane Library (http://www.thecochranelibrary.com/view/0/index.html), performed on October 19, 2010 using the search terms "Provenge®," "sipuleucel-T," or "APC8015," revealed two TA's. One TA, dated December 2005 and titled "Vaccines for metastatic hormone-refractory prostate cancer," was from the Canadian Coordinating Office for Health Technology Assessment (www.ccohta.ca). Two vaccines, Provenge® and GVAX, were assessed. The TA noted that Provenge® was not yet on the market in any country. The TA also commented that Provenge® is "safe and well-tolerated," "demonstrates a statistically significant survival benefit" and that future "clinical trials should compare Provenge® with the current treatment (Taxotere plus prednisone)."

The second TA, dated September 2007 and titled "Sipuleucel-T (Provenge®): Active cellular immunotherapy for advanced prostate cancer," was from the Canadian Agency for Drugs and Technologies in Health (http://www.cadth.ca/media/pdf/E0037_Sipuleucel-T_prostate_cancer_cetap_e.pdf). This TA, which focused only on sipuleucel-T, noted that the evidence so far indicated a survival benefit in men with androgen-independent prostate cancer but that these were preliminary results that need to be confirmed in future, larger clinical trials. In addition, the TA noted that future studies are necessary to evaluate the effectiveness and safety of sipuleucel-T in men with earlier stages of prostate cancer and in combination with other treatments for prostate cancer.

Another TA, dated April 2010 and titled "Special report: vaccines for the treatment of prostate cancer" was conducted by the Blue Cross Blue Shield Association Technology Assessment Evaluation Center. This assessment was performed and the report released just prior to the FDA approval of Provenge®. The report noted that Provenge® is one of only two "vaccines" that have progressed to Phase 3 clinical investigation and, given the preliminary nature of the evidence, Provenge® has demonstrated the "curious result" of an increase in overall survival but no impact on cancer progression.

In June 2010 CMS commissioned an external TA for this PDM through the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers Program. The Blue Cross Blue Shield Association Technology Assessment Evaluation Center performed the work.

Mark et al. prepared a final TA dated February 10, 2011 and titled "Outcomes of Sipuleucel-T Therapy." The TA addresses three key questions posed by CMS:

1. What is the evidence regarding the clinical outcomes of sipuleucel-T for its FDA-approved indication; asymptomatic or minimally symptomatic metastatic androgen-independent prostate cancer?
    1a. What is the evidence regarding the relationship between baseline patient characteristics, measurable characteristics of treatment such as cell number or immune response characteristics of patients, post-treatment factors, and sipuleucel-T on outcomes of treatment?
2. What is the level of evidence and summary of evidence for off label indications for sipuleucel-T?
    2a. For off label indications, what is the evidence regarding the relationship between baseline patient characteristics, measurable characteristics of treatment such as cell number or immune response characteristics of patients, post-treatment factors, and sipuleucel-T on outcomes of treatment?

1. What is the evidence regarding adverse events potentially attributable to the use of sipuleucel-T?

The authors conducted a search of the Medline, Embase and Cochrane Controlled Trials Register databases using the search terms “Provenge,” “sipuleucel,” “Dendreon,” “APC-8015,” “prostate,” “prostatic” and “dendritic cell.” Publically available documents from the FDA, clinicaltrial.gov and conference abstract websites were also searched. Articles or abstracts were selected for further review if they presented the results from randomized, controlled trials or case series studies, focused on the use of sipuleucel-T in patients with prostate cancer, and included at least one clinically relevant outcome of interest.

The quality of a comparative study was assessed using a process developed by the US Preventive Services Task Force. Studies were rated as good, fair or poor. The TA also rated the strength of the overall body of evidence using a system developed by AHRQ, which evaluates risk of bias, consistency, directness and precision. Evidence strength was given a grade of high, moderate, low or insufficient. For more detailed information about these two assessments please see the TA.

A brief summary of the results of the TA are presented below by key question:

1. What is the evidence regarding the clinical outcomes of sipuleucel-T for its FDA-approved indication; asymptomatic or minimally symptomatic metastatic androgen-independent prostate cancer?

Mark et al. evaluated evidence from three randomized, controlled trials that had been published in numerous source documents including FDA reviews and the peer-reviewed medical literature. They identified the trials as “IMPACT,” “D9901” and “D9902A.” They remarked that the numerous sources of documents introduced three concerns during the TA. The first concern was the potential for “discordant results seeming to arise out of what appears to be the same analysis. Such issues could arise from error, slight differences in the data used, such as different cutoff date, or minor selection criteria. We noticed several instances where calculations varied beyond the tenth place in a decimal calculation. We used the peer-reviewed publication value whenever there was discordance.”

The second concern was “the presentation of alternative or “sensitivity” analyses, which are variations on a particular analysis usually meant to support the validity of the primary analysis. These are sometimes problematic, because they are usually performed post-hoc, often incompletely described and presented, and may be inappropriate. There are many such analyses in the published materials we reviewed for this assessment. Presentation of all these analyses may give the impression that there is more evidence than there really is. Analyses based on the same data set are obviously highly correlated; the unmeasured biases of that study exist across all analyses. In these materials, it is evident that some analyses performed by FDA statisticians on the clinical trial data were meant to critique the validity of the sensitivity analyses performed by the sponsor. Points of contention raised by competing statistical analyses raise issues that may not be solvable but point to an underlying uncertainty in the conclusions of a particular analysis.” Given these caveats, the authors opted to focus on the principal results of the studies and simply summarize the results of the numerous sensitivity analyses. In this PDM, CMS will take an identical approach.

The last concern was that “the studies were not fully independent investigations, although they will be presented as such. Decisions regarding outcome measures, selection criteria, and analysis were made based on the findings of the earlier studies. For example, because study D9901 did not attain statistical significance for its original end point of progression-free survival, enrollment for study D9902A was terminated; thus, its sample size is smaller than originally planned. Because of results obtained from analyses of D9901 and D9902A, the principal outcome of IMPACT was changed to overall survival, and selection criteria for the study were altered.”

Mark et al. identified a number of issues with the study design, which was very similar for all three trials. The sipuleucel-T administered to patients originally in the placebo arm that experienced disease progression and were subsequently unblinded (the authors referred to this as frozen salvage product) was different from the sipuleucel-T administered to the patients randomized to the sipuleucel-T arm. As stated by the authors: "In addition to being prepared from cryopreserved cells, another difference between frozen salvage product and sipuleucel-T is that the frozen cells have never been exposed to circulating sipuleucel-T in the patient's body. In the treatment groups of the clinical trial, the cells extracted at the second and third leukapheresis sessions are drawn from subjects who have had prior exposure to sipuleucel-T from the first dose." This difference may have impacted the internal validity of the study. The lack of a truly inert placebo was another issue identified by the authors that may have impacted internal validity.

Given the concerns and issues just described, the quality of each of the three trials was rated as good. The TA also rated the strength of the overall body of evidence as "moderate" using a system developed by AHRQ. "The principal reason for the moderate grade is the risk of bias due to the unequal provision of subsequent treatments. The trial design resulted in a systematic bias against the control group due to a delay induced by treatment with frozen salvage product. The statistical methods used to account for subsequent treatments are limited in that time-dependent confounding effects cannot be accounted for."

Appendix B contains tables from the TA that show the survival results from each of the trials. Duration of follow-up in each trial was sufficient to follow patient survival outcome until at least 67% had died. Median survival difference between each arm was 4.1 months for the IMPACT study, 4.5 months in D9901 and 3.3 months in D9902A. The authors noted however that "in D9902A, survival times were shorter in both sipuleucel-T and placebo groups, such that the median survival time in the sipuleucel-T group was shorter than the placebo groups from the other 2 trials. There does not appear to be any difference in patient characteristics in this trial to explain this difference in survival times. However, given the relatively small sample size of the study, the result could be due to chance. The hazard ratio for death calculated from a Cox proportional hazard model shows a reduction in mortality for sipuleucel-T treated groups of 0.77, 0.59, and 0.79, from the IMPACT, D9901, and D9902A studies, respectively. These differences were statistically significant for the IMPACT and D9901, but not significant for the D9902A."

Appendix C contains a table from the TA that shows the results for the disease progression outcomes and other secondary outcomes from each of the trials. None of the results for the disease progression outcomes achieved statistical significance.

The TA considered the impact on health outcome of subsequent salvage treatment or chemotherapy after disease progression. In the IMPACT study 63.7% received salvage treatment while 75.6% and 66.7% received salvage treatment in D9901 and D9902A, respectively. In the IMPACT study the median survival for patients who received salvage treatment was 23.8 months compared to 11.6 months for those who did not. The authors noted that this "comparison should not be used to infer a potentially beneficial effect of frozen salvage product, because it is not randomized and is subject to survivor bias. Assignment to the frozen salvage product group is conditional on survival up to the point of receipt of that treatment, producing a survivor bias."

In each of the three studies some patients with disease progression from either the sipuleucel-T arm or the control arm subsequently received chemotherapy. The impact of docetaxel, which has shown a survival benefit in previous clinical trials, was assessed. For the IMPACT study, "a greater proportion of sipuleucel-T-treated patients received docetaxel chemotherapy (57.2 percent versus 50.3 percent), and they also received it earlier (median 7.2 months versus 9.6 months). In D9902A, slightly more sipuleucel-T treated-patients received docetaxel (38.6 percent versus 34.4 percent), but in D9901, more placebo-treated patients received docetaxel (47.6 percent versus 35.9 percent). The difference in median time to receipt of docetaxel in IMPACT might be partially explained by the use of frozen salvage product in the placebo group, which requires one month to administer."

Mark et al. noted the different types of analyses, and the results of these analyses, that were conducted to adjust for the potential confounding effects of the administration of docetaxel. "In one type of analysis, patients are removed ("censored") from the study upon docetaxel initiation. Assuming that the patients censored are similar to the patients not censored, such an analysis intends to estimate the survival of patients who did not receive docetaxel. This analysis of the IMPACT data showed a treatment effect hazard ratio of 0.649, which was statistically significant (p=0.009). Another analysis of IMPACT data using a time-dependent variable indicating the time of docetaxel use showed a hazard ratio of 0.777 which was also statistically significant (p=0.034). An analysis with time-dependent variables assumes that patients who receive docetaxel are similar to patients who do not receive docetaxel, and that their estimated survival is altered by some fixed magnitude upon receiving docetaxel treatment. Analyses of D9901 and D9902A, which are likely to be time-dependent analyses, show similar magnitudes of treatment hazard ratio of sipuleucel-T to the other analyses, but do not meet the standard level of statistical significance.

The authors expressed uncertainty that the analyses performed can fully account for all of the potential confounding effects of subsequent docetaxel treatment. Specifically, these analyses did not "account for potential differences between treatment regimens in terms of dose or length of treatment. The analyses require assumptions of the events which are not observable in the trial. The usual assumption of an analysis censoring subjects at the time of docetaxel use is that the censoring time provides no further information about the subjects' likelihood of future survival. Survival curves will be biased unless those who were censored for docetaxel use have similar expected survival to those who were not censored for docetaxel use. This assumption is implausible, since docetaxel is a treatment for disease progression. However, the effect of this bias on the estimate of the relative effect of sipuleucel-T on survival would depend on the degree of this bias in each treatment arm. It could be possible that each treatment arm is similarly affected by this bias, producing an unbiased estimate of treatment effect. Time-dependent analyses also assume that the change of exposure and its timing are not related to the probability of future survival." The TA noted that this analytic issue is called time-dependent confounding.

To summarize their assessment for this key question the authors stated that "all three studies showed improved median and 36-month survival of sipuleucel-T-treated subjects compared to placebo-treated subjects. In two of the studies, the difference met traditional levels of statistical significance. The third smaller study did not meet statistical significance. The third study showed overall shorter survival times, but chance or other unmeasured difference in study participants could explain the finding. There was no difference in disease progression end points. Analyses undertaken to account for potential confounding effects of subsequent treatments did not change the magnitude or statistical significance of the findings, but such methods may be limited in the ability to fully account for such effects."

> *1a. What is the evidence regarding the relationship between baseline patient characteristics, measurable characteristics of treatment such as cell number or immune response characteristics of patients, post-treatment factors, and sipuleucel-T on outcomes of treatment?*

In this question the authors were asked to assess the results of subgroup analyses. While acknowledging the potential benefits of conducting subgroup analyses such as the identification of treatment modifiers, the authors also stated the potential statistical limitations of such analyses including a lack of power to detect a real difference due to the small sample size of each subgroup. The authors noted that this problem was compounded by the "fairly small" size of the database from D9901 and from D9902A. "Thus it is unlikely that examination of subgroup effects in these trials would generate any definitive findings unless the underlying treatment interactions were extremely strong. Any suggestion of a subgroup effect in these analyses would require further research and confirmation." Therefore, while the authors presented the results of the subgroup analyses for the pooled efficacy databases, their opinion was that "the broad confidence intervals encompassing each subgroup hazard ratio preclude any conclusions or signals of subgroup treatment effects. It cannot be determined whether any large difference between the two hazard ratios between any pair of subgroups is due to random variation (chance) or a real interaction."

Mark et al. expressed a similar judgment upon examining the results of subgroup analyses for just the IMPACT efficacy database with one exception: the effect of patient age (i.e., younger than 65 years v. 65 years of age or older). However, as noted above, in the analysis of the pooled efficacy database, this difference in outcome by age group was not found hence the authors conclude that it is "inconclusive whether there is a true treatment interaction" based on age group.

In their assessment of cell product parameters and patient outcome the authors examined the association of survival with CD54 up-regulation ratio, total nucleated cell count and CD54 cell count. The only results available were from patients in the sipuleucel-T arm. Without the ability to compare these results to those obtained from patients in the control arm, it was not possible to differentiate "a treatment effect versus a characteristic associated with inherent survival."

The assessment of the association of patient immune response, as measured by antibody titer against T-cell proliferation to PA2024 or PAP, and patient outcome was based on results from only patients from the IMPACT study. The authors noted that there "were no associations between T-cell proliferation to PA2024 or PAP and survival. None of these analyses appear to have been adjusted for potential confounding variables."

Mark et al. concluded that "some analyses of product parameters and patient immune responses show an association between the characteristic and survival, but the clinical significance of these associations are unknown. Because the biologic mechanism of the therapeutic effect of sipuleucel-T is not fully understood, these analyses do not inform the question of the overall efficacy of sipuleucel-T. The quantity of data and the analyses performed so far are not sufficient to determine whether such product parameters or measures of patient immune response are clinically useful."

Finally, Mark et al. examined the efficacy results to "determine if there is an interaction of sipuleucel-T and post-treatment chemotherapy. That is, is there a differential effectiveness of sipuleucel-T depending on whether post-treatment chemotherapy is given or not?" The authors continue by stating that "Unfortunately, given the data and analysis available, this is difficult to determine. Examination of the survival curves of each initial and subsequent treatment group (sipuleucel-T/placebo, no docetaxel/docetaxel) may be biased by potential confounding and survival biases. The groups receiving post-progression docetaxel survive longer than the other groups because receiving such treatment was conditional on being alive to receive such treatment. If sipuleucel-T is effective, then it is effective in a context in which a substantial proportion of patients receive subsequent chemotherapy. Determination of the independent and/or interactive effects of sipuleucel-T and subsequent therapies would require further study using study designs where patients are randomized to subsequent treatments or data collection and analyses are performed which can account for time-dependent confounding variables."

2. What is the level of evidence and summary of evidence for off label indications for sipuleucel-T?

A formal rating of the quality of each study was not performed given the lack of comparative studies to rate. Dr. Mark et al. noted that the peer-reviewed and published studies that investigated the use of sipuleucel-T in patients without both metastatic and castration resistant prostate cancer "were early Phase I and II studies which did not have control groups. They were largely intended to assess potential biologic activity, immune response, and safety, and thus were not intended to provide definitive evidence for efficacy. They may have not been designed or conceived with strict treatment indications in mind. The shortcomings of those studies in determining efficacy should be viewed in this light. In addition, the dose and scheduling of treatment differed from the three RCTs previously reviewed for the on-label indication. The manufacturing process and quality control criteria may have differed from the currently available treatment." One abstract was found of a randomized, controlled trial but there was minimal detail available about the patient population and results; this study has yet to be published in a peer-reviewed article.

In conclusion, the authors stated that there "is insufficient evidence to evaluate the outcomes for off-label indications.".

2a. For off label indications, what is the evidence regarding the relationship between baseline patient characteristics, measurable characteristics of treatment such as cell number or immune response characteristics of patients, post-treatment factors, and sipuleucel-T on outcomes of treatment?

The authors succinctly noted that "Since none of the studies provide evidence of efficacy of sipuleucel-T for off label indications, this question is moot."

3. *What is the evidence regarding adverse events potentially attributable to the use of sipuleucel-T?*

Marks et al. used the pooled safety analysis from the FDA Clinical Review to assess adverse events. Thus, the TA's safety analysis was based on the 601 patients treated with sipuleucel-T and 303 placebo-treated patients. The authors stated that given the length of the safety analysis report in the FDA's clinical review, the TA focuses on "some of the issues analyzed in the review we judged to be relevant: 1) deaths occurring proximate in time to treatment; 2) nonfatal serious adverse events; 3) cerebrovascular events; 4) infections; and 5) infusion-related adverse events." In addition, "Using the questions proposed to evaluate the quality of reporting harms based on the McMaster Quality Assessment Scale for Harms, based on the description of adverse events reporting from the protocol document for the IMPACT trial and the FDA Clinical Review, we judged that all 6 questions could be answered affirmatively and thus the adverse event reporting in this document was of good quality."

The authors introduced a number of reasons that increased the complexity of assessing the adverse effects of sipuleucel -T. The first reason concerned the advanced age of the typical patient with metastatic, castration-resistant prostate cancer. Comorbidities are common in this age group. The authors noted that "As patients are followed for a survival end point, as disease progresses it would become increasingly difficult to attribute any particular event to the patients' existing comorbidities, progressive cancer, sipuleucel-T, or other subsequent treatments. In all of the randomized clinical trials, after progression of prostate cancer (in IMPACT) or after 16 weeks (in D9901 and D9902A), adverse events, with the exception of cerebrovascular events (CVEs), were only collected if they were thought by the investigators to be related to sipuleucel-T treatment. Since the studies became unblinded at the time of disease progression, such a judgment of causality could be biased."

In the authors' opinion the lack of a truly inert placebo was a second reason for increased complexity. Patients in the control arm of each study "were subjected to leukapheresis procedures and received an infusion of cultured but untreated cells. Thus any adverse effects caused by procedures in common between the treated and placebo groups might be balanced in the two groups. In the usual clinical trial with an inert placebo, an equal incidence of an adverse event in active and placebo groups implies that the event is due to inherent baseline risk, natural history, or psychological effects. This conclusion should not be made in these clinical trials, particularly for types of events that are suspected or known to be caused by infusions. If, for example, contaminated infusions cause an equal incidence of bacterial infection in both sipuleucel-T and placebo groups, it should not be concluded that sipuleucel-T does not cause bacterial infection."

The third reason for increased complexity: "after progression a large proportion of placebo-treated patients received frozen sipuleucel-T salvage treatment. We could not locate reports of the adverse events associated with frozen salvage treatment. It is unknown whether the potential risks of standard sipuleucel-T may occur with frozen sipuleucel-T salvage product. In addition, as reported previously, many patients in both groups received chemotherapy. Given these multiple confounding effects, it is very difficult to tell if events occurring distant in time to the initial treatment with sipuleucel-T or placebo can accurately be attributed to sipuleucel-T."

The authors concluded that "there are a few solid conclusions that can be reached." However, they did identify two adverse events, infusion reactions and infections, which have an association with sipuleucel-T treatment. They stated that sipuleucel-T "can cause symptoms consistent with an infusion reaction" given the greater frequency of infusions reactions in the sipuleucel-T group compared to the placebo group as well as the temporal proximity of infusion reactions to the administration of sipuleucel-T. They also noted that infections during sipuleucel-T treatment are "probably in relation to leukapheresis and infusion procedures. Catheter-related infections are attributable to sipuleucel-T treatment. Some infections proximate in time to infusion are possibly related to sipuleucel-T treatment. Attribution is difficult because the control groups in the RCTs also underwent leukapheresis and infusion procedures. Contaminated infusion product has been documented."

Beyond these two types of serious adverse events, “it is unclear whether there is an association with sipuleucel-T treatment. CVEs were a particular focus of attention, and although rates were slightly higher, it is not possible with the data available to determine causality. No associations with product parameters or interactions with patient characteristics were identified.”

Overall Conclusions

In their overall conclusion for the TA the authors stated that “Three randomized clinical trials of sipuleucel-T are consistent with longer overall survival in patients meeting the FDA-labeled indication. This conclusion is tempered by consideration of a trial design with inherent potential for confounding due to systematic differences in post-progression treatment, making the estimate of the quantity of benefit less certain. This treatment effect occurs in the context of use of post-progression chemotherapy. There is insufficient evidence regarding potential interactions, associations with characteristics of the product, and interactions with other treatment. There is insufficient evidence for any off-label indication. Sipuleucel-T can cause infusion reactions and infections.”

“Interpretation of the existing clinical trials of sipuleucel-T was hampered by a study design that had the original intended purpose of assessing progression-free survival in an objective manner. This dictated measures such as blinding and placebo in order to avoid bias in the assessment of outcome. The likely presence of time-varying subsequent treatment and confounding adds further complexities. Since it appears that sipuleucel-T has little or no effect in delaying measurable disease progression, it would be important for future trials to be robustly designed for a survival end point. Although it is not possible to dictate all possible treatments being employed in clinical trials, particularly as patients’ disease progresses, study designs should avoid the potential for systematic biases in the use of post-progression treatments and ensure an equal standard of care for patients in all treatment arms.”

“Because the effect of sipuleucel-T is not apparent early in the course of disease after treatment and only in the context of a substantial amount of eventual chemotherapeutic treatment, it would be important to understand the existence of and nature of interactions between sipuleucel-T and subsequent treatments. The current existing analyses are insufficient to know to what degree sipuleucel-T is effective in the absence of chemotherapy or depends on chemotherapy to demonstrate improvement in survival. Such information is critical for decisions physicians and patients need to make as they plan how to treat the patient’s cancer. Future clinical trials with properly designed treatment arms and data collection may be able to determine these interactions.”

3. Internal technology assessment

CMS performed a literature search using PubMed on October 15, 2010 with the search terms “Provenge,” or “sipuleucel-T,” or “APC8015.” The following limitations were applied: Humans, Clinical Trial, Meta-Analysis, Practice Guideline, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, and Multicenter Study. Ten literature articles were identified due to this search. Eight articles addressed the on-label use of Provenge while the remaining two addressed off-label use.

On label Use

Eight articles were found that focus on on-label use. Three of the eight articles (Small, 2006; Higano, 2009; Kantoff, 2010) presented results from randomized, controlled trials. These trials comprised the majority of the evidence that FDA used as the basis for its decision. CMS’ presentation of these trials is located in the Evidence Summary below. The remaining five articles are not addressed in this PDM because they either concerned an early (Phase 1 or 2), uncontrolled study that did not assess a health outcome as its primary endpoint (Small, 2000; Burch, 2000; Burch, 2004) or presented only preliminary results of a Phase 3 study (Lee, 2003; Schellhammer, 2005) that were presented completely in a subsequent article by Small et al.., 2006.

Off label Use

No Phase 3 studies were found during the literature search.

Evidence Summary

On label Use

Small EJ, et al. Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic, asymptomatic hormone refractory prostate cancer. *Journal of Clinical Oncology* 2006;24:3089-3094.

Note: This article presents the results of the trial labeled as D9901 in the FDA clinical review.

Small, et al. presented the results of a US-based, multicenter, double-blind, placebo-controlled, randomized (2 sipuleucel -T:1 placebo) Phase 3 trial in patients with metastatic, castration-resistant prostate cancer. Patients had to have radiologic evidence of metastases, a serum testosterone less than 50 ng/dl, and an ECOG performance status of 0 or 1. Concurrent bisphosphonates treatment was permitted but not systemic corticosteroids. Patients with cancer-related bone pain or who were taking opioid analgesics for cancer pain were excluded. Patients randomized to the placebo arm who subsequently were unblinded due to disease progression were eligible for treatment with sipuleucel-T as salvage therapy. Treatment with any type of anti-cancer therapy was prohibited until the primary efficacy endpoint was met. At that time, each patient was treated by his own physician.

Sipuleucel-T or placebo was prepared after each of three leukaphereses. Sipuleucel-T was manufactured by the procedure presented in the Background section of this PDM. Placebo consisted of the reinfusion of only one-third of the APCs isolated during leukapheresis without any exposure to PA2024. The remaining APCs were frozen to be used in the patient if he experienced disease progression. At that time, the APCs were thawed and combined with PA2024. This product was referred to as APC8015F. Sipuleucel-T or placebo was administered intravenously during weeks 0, 2 and 4 with acetaminophen and diphenhydramine for premedication.

The primary efficacy endpoint was time to progression (TTP) where TTP was defined as radiologic evidence of progression (an increase of greater than 50% in measurable disease, clear worsening of nonmeasurable disease, and/or appearance of two new lesions on bone scan), onset of new cancer-related pain associated with radiologic evidence for that pain, or onset of known prostate cancer-related complications such as spinal cord compression, pathologic fracture or nerve root compression. An intent-to-treat analysis was the primary efficacy analysis. Patients were also followed for survival and treatment-related adverse events for 36 months after randomization.

In 19 study centers, 127 patients received at least one infusion (82 in the sipuleucel-T arm and 45 in the placebo arm); 95% received all three infusions. The median age was 73 years (range 47-85) in the sipuleucel-T arm and 71 years (range 50-86) in the placebo arm. Eighty-nine percent and 93% of patients in the sipuleucel-T and placebo arms, respectively, were white. There were no statistically significant differences between the two groups with regards to patient characteristics.

Ninety percent of patients experienced disease progression in the study. All but one patient experienced disease progression prior to death. The median TTP was 11.7 weeks (95% CI, 9.1 to 16.6) for patients in the sipuleucel-T arm and 10 weeks (95%, 8.7 to 13.1) for patients in the placebo arm ($p = 0.052$; HR, 1.45; 95%CI, 0.99 to 2.11). After the patient's disease progressed, 55.7% of patients in the sipuleucel-T arm and 52.4% of patients in the placebo arm received chemotherapy. A greater percentage of patients in the placebo arm received docetaxel-based chemotherapy for disease progression than in the sipuleucel-T arm (47.6% v. 35.9%).

All 127 patients were included in the analysis for overall survival. The median OS was 25.9 months (95%, 20 to 31.9) in the sipuleucel-T arm and 21.4 months (95%, 12.3 to 25.8) for patients in the placebo arm (p = 0.01; HR, 1.70; 95%CI, 1.13 to 2.56). The estimated survival rate at 36 months was 34% in the sipuleucel-T arm and 11% in the placebo arm (p = 0.005). The authors tested the robustness of this survival benefit for sipuleucel-T by adjusting the OS analysis using five clinical variables identified in a regression analysis (lactate dehydrogenase, PSA, number of bone metastases, body weight and localization of disease). The result of the original OS analysis remained statistically significant after this adjusted OS analysis (P < 0.002; HR, 2.12; 95%CI, 1.31 to 3.44).

Patients in the sipuleucel-T arm experienced more episodes of rigors (59.8% v. 8.9%), fever (29.3% v. 2.2%) and tremor (9.8% v. 0%) compared to patients in the placebo arm. In each arm 24.4% of patients experienced a severe adverse event. In the sipuleucel-T arm 4.9% of patients experienced severe dyspnea versus 2.2% in the placebo arm. In the sipuleucel-T arm 4.9% of patients experienced severe rigors versus 0% in the placebo arm.

The authors noted that sipuleucel-T did not show a statistically significant tumor response (i.e., an improvement in TTP) compared to placebo in asymptomatic patients but did show a statistically significant improvement in the secondary efficacy endpoint of OS compared to placebo. They also observed in both arms a rapid increase in the number of patients who experienced disease progression within the first two months of the study. After that time point, the pace of onset of disease progression for patients in the sipuleucel-T arm decreased compared to that for patients who received placebo. The authors noted that earlier studies of sipuleucel-T "suggested that maximum T-cell reactivity takes 8 to 10 weeks to achieve, so some patients may have developed progression disease before the treatment achieved its biologic effects." They postulated that the "rapid development of progression may make TTP an unsuitable intermediate marker of survival when the putative biologic effects of the investigational agent tend to occur after progression. An immunotherapeutic approach such as sipuleucel-T may therefore have more gradual antitumor effects that will be more apparent in patients with less aggressive disease."

The authors concluded that sipuleucel-T may provide a survival advantage to patients with asymptomatic prostate cancer but that additional studies are needed for confirmation.

Higano CS, et al. Integrated data from 2 randomized, double-blind, placebo-controlled, phase 3 trials of active cellular immunotherapy with sipuleucel-T in advanced prostate cancer. *Cancer* 2009;115:3670–9.

Note: This article presents the results of a pooled analysis of data from two trials: the Phase 3 trial labeled as D9901 and the Phase 3 trial labeled as D9902A in the FDA clinical review. Small, et al. published the results of D9901 (see above). The protocol for D9902A was identical to that for, and conducted contemporaneously to, the protocol for D9901. D9902A was stopped prematurely after the enrollment of 98 patients due to the initial disease progression results but prior to the availability of survival results from D9901.

Higano, et al. present the results of an integrated efficacy analysis of the D9901 and the D9902A data. An integrated analysis of the intent-to-treat population was conducted in order to assess the safety and efficacy of sipuleucel-T using a larger sample size.

The sample size for the integrated analysis was 225 with 147 patients in the sipuleucel-T group and 78 patients in the placebo group. The median age was 72 years (range 47 to 85) and 71 years (range 50 to 87) in the sipuleucel-T and placebo groups, respectively. The majority of patients were white; 89.8% in the sipuleucel-T group and 93.6% in the placebo group. There were no reported statistically significant differences between the two groups with regards to patient characteristics.

All 225 patients were included in the integrated efficacy analysis. The median TTP was 11.1 weeks (95% CI, 10 to 16.3) for patients in the sipuleucel-T arm and 9.7 weeks (95%, 8.7 to 13.3) for patients in the placebo arm (p = 0.11; HR, 1.26; 95%CI, 0.95 to 1.68). Seventy-two percent of patients from the placebo group received salvage treatment with APC8015F upon disease progression. In addition, 57% of patients in the sipuleucel-T arm and 58% of patients in the placebo arm received chemotherapy. A greater percentage of patients in the placebo arm received docetaxel-based chemotherapy for disease progression than in the sipuleucel-T arm (40% v. 35%) but the difference was not statistically significant.

The median OS was 23.2 months (95%, 19 to 31) in the sipuleucel-T arm and 18.9 months (95%, 13.5 to 25.3) for patients in the placebo arm (p = 0.01; HR, 1.50; 95%CI, 1.10 to 2.05). The authors tested the robustness of this survival benefit for sipuleucel-T by adjusting the OS analysis using the same five clinical variables identified in a regression analysis of D9901 (lactate dehydrogenase, PSA, number of bone metastases, body weight and localization of disease). The result of the original OS analysis remained statistically significant after this adjusted OS analysis (P<0.001; HR, 1.86; 95%CI, 1.31 to 2.63).

A similar incidence of adverse events was experienced by both groups (98.6% for sipuleucel-T patients and 96.1% for placebo patients). A higher rate of chills, fever, headache, dyspnea, vomiting and tremor was found for the sipuleucel-T group than for the placebo group. The severity of these adverse events was "primarily grade 1 and 2, with a duration of 1 to 2 days." The frequency of serious adverse events was similar between the two groups (23.8% for sipuleucel-T and 22.4% for placebo). Incidence of cerebrovascular events reported as an adverse event or as a cause of death was a 7.5% in the sipuleucel-T group and 2.6% in the placebo group.

Based on the results of the integrated analysis, the authors noted "a trend toward a delay in the time to disease progression." The authors stated that additional studies are underway to assess the nature of the increased incidence of cerebrovascular events found in this study. The authors concluded that the results of the integrated analysis show a "generally modest toxicity profile" as well as "suggest that sipuleucel-T may prolong overall survival." This "suggests a favorable risk-benefit ratio for sipuleucel-T" in asymptomatic patients.

Kantoff PW, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *New England Journal of Medicine* 2010;363:411-422.

Note: This article presents the results of the Phase 3 trial labeled as D9902B in the FDA clinical review. This study is also referred to as the Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) study.

The protocol design for D9902B was identical to protocol for D9902A (which, again, was identical to that for D9901) with the following revisions (made prior to unblinding) based on the results of D9901 and D9902A:

- The inclusion of minimally symptomatic patients. The methodology section of the article did not define the term "minimally symptomatic."
- OS (defined as death from any cause) was the primary efficacy endpoint, which replaced the original co-primary endpoints of time to disease progression and time to disease-related pain; time to disease progression became a secondary endpoint
- The inclusion of men with prostate cancer with any Gleason score
- A planned interim analysis with incorporation of procedures to adjust the final efficacy analysis

Appendix D contains an extensive list of the inclusion and exclusion criteria for D9902B.

In 75 study centers in the United States and Canada, 512 patients were enrolled and 497 of these received at least one infusion (330 in the sipuleucel-T arm and 167 in the placebo arm); 92.2% received all three infusions. The median age for the 512 patients who were enrolled was 72 years (range 49-91) in the sipuleucel-T arm and 70 years (range 40-89) in the placebo arm. Eighty-nine percent and 91% of patients in the sipuleucel-T and placebo arms, respectively, were white. The percentage of patients with a baseline pain score of zero was 51.5% in the sipuleucel-T arm and 52.6% in the placebo arm. The percentage of patients with a baseline pain score of zero or above was 48.5% in the sipuleucel-T arm and 47.4% in the placebo arm. The article does not indicate that there were any statistically significant differences between the two arms with regards to patient characteristics.

All 512 enrolled patients were included in the analysis for OS. By the pre-specified cut-off date (median follow-up of 34.1 months), 61.6% of patients who received sipuleucel-T had died and 70.8% of patients in the placebo arm had died. The median OS was 25.8 months in the sipuleucel-T arm and 21.7 months for patients in the placebo arm (hazard ratio, 0.78; 95% CI, 0.61 to 0.98; P = 0.03). An analysis was performed to ascertain the impact of subsequent docetaxel therapy on the primary efficacy analysis. This analysis revealed a consistent treatment effect in favor of sipuleucel-T (hazard ratio, 0.65; 95% CI, 0.47 to 0.90; P=0.009).

The median TTP was 14.6 weeks (95% CI, 9.1 to 16.6) for patients in the sipuleucel-T arm and 14.4 weeks for patients in the placebo arm (hazard ratio, 0.95; 95% CI, 0.77 to 1.17; P = 0.63).

After the patient's disease progressed, 81.8% of patients in the sipuleucel-T arm and 73.1% of patients in the placebo arm received anticancer therapy (not including APC8015F). A slightly greater percentage of patients in the sipuleucel-T arm received docetaxel-based chemotherapy for disease progression than in the placebo arm (57.2% v. 50.3%). The median time to administration of docetaxel was 12.3 months in patients in the sipuleucel-T arm and 13.9 months in the placebo arm.

For patients in the placebo arm, 63.7% received salvage therapy with APC8015F at some point after disease progression. Forty-nine percent received APC8015F prior to other types of anticancer treatment.

Ninety-eight percent of the 506 patients in the safety database experienced an adverse event. These adverse events were reported as mild to moderate (Grade 1 or 2) for 65.2% of these patients. The most common adverse events in the sipuleucel-T arm compared to the placebo arm were chills, fever, headache, influenza-like illness, muscle aches, hypertension, groin pain and excessive sweating. Chills, fever, fatigue, nausea and headache were the most commonly reported adverse events within one day of infusion in the sipuleucel-T arm. The most common adverse events in the placebo arm compared to the sipuleucel-T arm were anorexia, anxiety, depression, flank pain, contusion and hydronephrosis.

A greater percentage of patients in the sipuleucel-T arm had Grade 3 or more severe adverse events within one day of infusion compared to the placebo arm (6.8% v. 1.8%). Reported Grade 3 adverse events included chills, fatigue, back pain, hypertension, hypokalemia and muscular weakness. Intravenous-associated bacteremia was the one reported Grade 4 adverse event. In the sipuleucel-T arm, 2.4% of patients experienced a cerebrovascular event compared to 1.8% of patients in the placebo arm; this difference was not statistically significant.

The authors noted that the results from this study "are consistent with and confirm the findings of a randomized trial, in which the sipuleucel-T group had a 3-year survival rate of 34.1%, a median increase in survival of 4.5 months, and a median survival of 25.9 months (25.8 months in our study)." This second randomized trial referred to above is D9901. The authors also state that "the selection of patients who received docetaxel may have confounded the estimation of the docetaxel effect. Nevertheless, sensitivity analyses did not provide evidence that between-group differences in the use of docetaxel could account for the observed treatment difference with respect to overall survival."

The authors concluded that "sipuleucel-T prolonged survival among men with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer. However, no significant effect on the time to objective disease progression was observed."

Off label Use

No Phase 3 trials were identified.

U.S. Food Drug Administration Review

The initial BLA was submitted and reviewed by FDA in 2006. An FDA advisory committee meeting, which was held in 2007 during the review period, issued a positive recommendation. The FDA declined to allow licensing of sipuleucel-T due to the small sample size of one Phase 3 trial (D9901) and the "lack of statistical persuasiveness." As noted in the complete response letter, FDA required the submission of efficacy data from an ongoing Phase 3 trial (D9902B) prior to issuing a licensure decision.

Dendreon resubmitted the BLA for Provenge in 2009. The FDA's clinical review was accessed from the FDA website. In the clinical review FDA assessed efficacy based on three clinical trials: D9901, D9902A and D9902B. These trials had a total of 737 patients with asymptomatic or mildly symptomatic, castration-resistant, metastatic prostate cancer who were randomized to the sipuleucel-T arm or to the control arm in a 2:1 ratio. A total of 488 patients were randomized to the sipuleucel-T arm and 249 patients to the control arm. A patient originally randomized to the control arm was eligible to receive an altered version of sipuleucel-T upon unblinding. This version of sipuleucel-T consisted of cryopreserved APC that was thawed and combined with PA2024 antigen.

Efficacy Assessment

D9902B had a total sample size of 512 with 341 patients randomized to receive sipuleucel-T. FDA considered this trial to be the pivotal study for the BLA. D9902B demonstrated a median overall survival (OS) of 25.8 months in the sipuleucel-T arm and 21.7 months in the control arm for a median increase in OS of 4.1 months for patients who received sipuleucel-T. This result was statistically significant ($p = 0.032$; HR, 0.775; 95%CI, 0.614 to 0.979). FDA stated that this is a "clinically meaningful improvement" as well. Of note, the original protocol included only asymptomatic (i.e., experiencing no pain) patients and the primary efficacy endpoint was time to disease progression. The protocol was subsequently altered in mid-study to permit the inclusion of patients with mildly symptomatic disease and to change the primary efficacy endpoint to OS. Mildly symptomatic disease was defined via the exclusion criteria. Specifically as stated in the FDA's clinical review, the exclusion criteria prevented patients with the following condition(s) from enrolling in the trial: "moderately or severely symptomatic disease, as defined by either criterion:

- Requirement for opioid analgesic within 21 days prior to registration
- Average weekly pain score of ≥4 on a 10-point Visual Analog Scale (VAS) on the Registration Pain Log."

D9901, considered by the FDA to be a supportive trial, had a total sample size of 127; 82 patients received sipuleucel-T. The primary efficacy endpoint was time to disease progression, which was 11 weeks in the sipuleucel-T arm and 9.1 weeks in the control arm for a median increase in time to progression of 1.9 weeks in patients who received sipuleucel-T. This result was not statistically significant. This study also examined OS as a secondary endpoint and showed results that were similar to those demonstrated in D9902B: 25.9 months in the sipuleucel-T arm and 21.4 months in the control arm ($p= 0.01$; HR, 0.568; 95%CI, 0.388 to 0.884).

The efficacy results for D9902A, which was terminated prematurely after a total of 98 patients were randomized (65 received sipuleucel-T) due to the poor efficacy results from D9901, differed substantially from those of the previous studies; the OS was 19 months in the sipuleucel-T arm and 15.7 months in the control arm. These results were not statistically significant. As with D9901, OS was not the primary efficacy endpoint for D9902A.

FDA performed an integrated analysis of efficacy, based on the data from D9902B, D9901, and D9902A, as presented in the FDA document titled "Summary Basis for Regulatory Action" (SBA). In this integrated efficacy analysis the median OS was 25.4 months for patients in the sipuleucel-T arm and 21.5 months in the control arm for a median improvement in OS of 3.9 months for patients who received sipuleucel-T ($p = 0.0009$; HR, 0.734; 95%CI, 0.612 to 0.881). No statistically significant differences were found in other efficacy endpoints such as time to disease progression or progression free survival. In its clinical review FDA noted the lack of correlation between OS and tumor response and stated that it "may be the result of difficulty in the radiological assessment of metastases to bone and lymph nodes."

Additional analyses of the data from D9902B were conducted by Dendreon for FDA. Subgroup analyses of OS were performed based on various demographic and baseline characteristics that were selected because of their possible prognostic impact on OS. Notable findings included:

- Fairly well balanced" patient characteristics between the two arms. More patients in the sipuleucel-T arm received chemotherapy prior to entry into the study however the number of patients was too small to permit a meaningful analysis of the impact of this imbalance.
- An OS benefit for the patients in the sipuleucel-T arm was consistently observed in all of the subgroups except for those who were younger than 65 years of age where there was a trend toward an improved OS for those in the control arm. Upon conducting additionally exploratory analyses, FDA concluded that this effect most likely resulted from chance due to the impact of multiple comparisons during subgroup analysis.

FDA reported the results of numerous sensitivity analyses of the data from D9902B. Of particular note were the results of sensitivity analyses conducted to evaluate the impact on the efficacy analysis of subsequent treatments in patients who experienced progression of their prostate cancer (a.k.a., salvage treatment). The analyses focused on two potential subsequent salvage treatments: 1) the administration of docetaxel in patients from the sipuleucel-T arm or from the control arm and 2) the administration of a slight variation of sipuleucel-T (produced from the activation of frozen cells previously collected from one leukapheresis rather than from three distinct leukaphereses) to patients from the control arm. Overall, FDA concluded that the analyses were "insufficient to support any conclusions" due to non-randomization and probable selection bias during the application of the salvage treatment.

FDA's clinical review of the efficacy of sipuleucel-T concluded that "D9902B, supported by the results of D9901 and D9902A, meets the regulatory standard for a single trial that provides the substantial evidence of effectiveness necessary to support a marketing approval." The FDA noted the decision was based on the results of only one adequate and well-controlled trial, which is contrary to the usual standard of requiring two such trials as stated in FDA guidance. FDA justified its decision based on the position that "a second study would be neither ethical nor feasible" in the US, that D9902B was of sufficient sample size and had "results that were consistent in multiple sensitivity analyses and across numerous subgroup analyses," and that the results were supported by two additional Phase 3 trials (i.e., D9901 and D9902A).

Safety Assessment

For their safety review FDA focused on the results from four clinical trials: D9901, D9902A, D9902B and P-11. The first three trials studied patients with metastatic, castrate-resistant prostate cancer while the last trial studied patients with earlier stage prostate cancer (a rising PSA after radical prostatectomy). The results from study P-11 were included in order to enhance the size of the safety database, which "permits a more reliable estimate of the incidence of common adverse events" and "facilitates the assessment of rare adverse events." FDA justified the pooling of the databases by the fact that all four trials "were sufficiently similar in design and results." Thus, a total of 904 patients who were randomized to receive either sipuleucel-T or control were evaluated for adverse events. Major findings from the safety assessment included:

- Patients in the control arm received non-activated cells rather than a true placebo. A true placebo would not be expected to cause adverse effects while cells, although non-activated, could cause adverse effects. In addition, just as for patients who ultimately received sipuleucel-T, patients in the control arm had to undergo leukapheresis (with all of the potential adverse effects of this procedure) in order to harvest their cells.
- The FDA identified a limitation to the safety database due to the small number of African Americans who were studied. Only 5.8% of the patients in the database were African American, which is a significant concern given that African American men have the highest incidence of prostate cancer and death from prostate cancer in the United States.
- 98.3% of patients in the sipuleucel-T arm and 96% of patients in the control arm experienced an adverse event. 67% of these occurrences were mild or moderate in severity and resolved within 48 hours. In their clinical review FDA stated that this "frequency of adverse events reflects the serious underlying disease, the complex background co-morbidities in the study population, the relatively complex study procedures (i.e., the leukaphereses and infusions), and the risks solely due to the study agents (sipuleucel-T and placebo)."
- Chills, fatigue, fever, back pain and nausea were the most common adverse events (i.e., occurred in 20% or more of patients who received sipuleucel-T).
- In the sipuleucel-T group 79.4% had an adverse event within one day of infusion compared to just 48.8% in the control group. FDA stated that most of these adverse events are consistent with the definition of an acute infusion reaction.
- The rate of nonfatal serious adverse events was 24% in the sipuleucel-T arm and 25.1% in the control arm.
- Patients who received sipuleucel-T experienced a higher rate of respiratory adverse events (for example, shortness of breath or a low level of oxygen in the blood) within one day of infusion compared to the control group. FDA stated that respiratory adverse events "appear to be infusion reactions directly related to the administration of sipuleucel-T" and recommended close monitoring of patients during the infusion.
- The mortality rate was 53% in the sipuleucel-T arm and 61.7% in the control arm. Disease progression was the most common reason for death.
- The rate of cerebrovascular events was 4% in the sipuleucel-T arm and 2.9% in the control arm. In its examination of this difference in cerebrovascular events FDA noted that, compared to the control group, the sipuleucel-T group had a higher percentage of patients 70 years of age or older with a history of cerebrovascular disease and/or hypertension. The rate of death associated with a cerebrovascular event was 1.3% in the sipuleucel-T arm and 0.7% in the control arm. The differences were not statistically significant. FDA noted that there were "multiple confounding factors which could have contributed to these differences in the incidence of both fatal and total" cerebrovascular events.

FDA concluded that sipuleucel-T was "relatively well tolerated without significant toxicities."

4. MEDCAC

On November 17, 2010, the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) met to discuss the body of evidence, hear presentations and public comment, and make recommendations to CMS regarding currently available evidence on the impact of labeled and unlabeled use of autologous cellular immunotherapy treatment on health outcomes of Medicare beneficiaries with castrate-resistant metastatic prostate cancer.

The voting questions were presented to the audience prior to the presentation of evidence from invited presenters. The voting questions, meeting agenda, invited presenters, and a speaker list may be found at http://www.cms.gov/medicare-coverage-database/details/medcac-meeting-details.aspx?MEDCACId=56&fromdb=true. Following the presentations from the two invited speakers, eight presentations from scheduled public commenters occurred. Following the scheduled public comments, members of the public were invited to speak. Many questions to the presenters were centered on clarification of the evidence presented. In general, the panel found intermediate confidence on the evidence for labeled use, and very low confidence on the evidence for off label use.

The voting questions and results as well as discussion questions may be found at: http://www.cms.gov/medicare-coverage-database/details/medcac-meeting-details.aspx?MEDCACId=56&fromdb=true. The specific question addressing off label use stated, "How confident are you that these conclusions are generalizable to unlabeled use in:

a. Patients whose prostate cancer has not metastasized?
b. Patients who have metastatic, castrate resistant disease and symptoms more severe than minimally symptomatic?
c. Patients who have metastatic prostate cancer but who have not failed hormonal therapy?

The mean number calculated from the answers provided by the voting MEDCAC members, on a scale of one to five with one designating “low confidence” and five designating “high confidence” was:

a. 1.1
b. 1.4
c. 1.2

The panelists discussed the last three questions in the order they were presented. The first focused on whether or not there is adequate evidence to identify patients who are more likely or less likely to respond favorably to autologous cellular immunotherapy treatment based on baseline clinical characteristics. The second question asked about evidence gaps for the FDA-labeled indication and for off-label use. The third question asked the panel members to address the clinical study designs that would adequately address any evidence gaps. The discussion is contained in the official transcript that may be found at http://www.cms.gov/faca/downloads/id56c.pdf .

5. Evidence-based guidelines

An Internet-based search of www.guideline.gov (i.e., the National Guideline Clearinghouse) using the search terms “Provenge®,” “sipuleucel-T,” or “APC8015” did not reveal any product-specific guidelines.

A number of disease-specific guidelines that addressed Provenge® were found. A guideline dated April 2010 by the European Association of Urology and titled “Guidelines on Prostate Cancer” was found via a general search of the Internet. With regards to Provenge®, this guideline briefly noted the significant overall survival benefit associated with Provenge® in the absence of a change in PSA level or an impact on progression-free survival as well as “a possible future for vaccination, particularly as tolerability was very acceptable (no grade 3, and only transient grade 1 or 2 vaccine -related adverse events).

The National Comprehensive Cancer Network (NCCN) has an evidence-based clinical practice guideline for prostate cancer that was recently updated to include the FDA approval of Provenge®. The NCCN guideline added sipuleucel-T as an option for salvage therapy for patients with castration-recurrent prostate cancer who have studies positive for metastases. NCCN assigned this recommendation as a “category one,” which means that the “recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.” The NCCN further states 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.” Of note, an ECOG performance status score of greater than or equal to two was a key exclusion criterion in D9902B. In the guideline, additional treatment options for this population of patients are docetaxel and steroids, secondary androgen depletion therapy, mitoxantrone and steroids, palliative radiotherapy or radionucleide and/or bisphosphonates for symptomatic bone metastases.

6. Professional Society Position Statements

We expect to receive professional society position statements on the proposed decision.

7. Expert Opinion

CMS sought and received expert opinion through the TA and MEDCAC processes. CMS also met with Dendreon Corporation, the manufacturer, and its physician representatives where an overview of the pivotal clinical trials was presented and aspects of the post marketing study were discussed. (See appendix E)

8. Public Comments

Initial 30 day comment period

CMS requested public comments on the evidence regarding the effects of autologous cellular immunotherapy treatment on health outcomes in patients with metastatic prostate cancer. Public comments sometimes cite the published clinical evidence and give CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision.

CMS received 657 public comments on autologous cellular immunotherapy treatment of metastatic prostate cancer. We reviewed the comments in their entirety. Sixty-seven (10.1%) of the comments were submitted by physicians and 23 (3.5%) were submitted by other health care providers. Additionally, 55 (8.4%) comments were submitted by patients, 18 (2.7%) by researchers or investigators, 10 (1.5%) by attorneys or law firms, and 15 (2.3%) by industry representatives or investors. Forty -four (8.2%) of the comments were received from representatives of professional groups and organizations or advocacy groups, and 455 (69.3%) comments were submitted by the general public, including friends and relatives of Medicare beneficiaries. Some commenters submitted via a legal representative to preserve anonymity in light of alleged death threats. Some commenters alleged that persons were spreading unfounded rumors while attempting to manipulate the stock price of Dendreon. Some commenters appear to have submitted under false identity, e.g. as “J. Mengala MD/PHD/VDRL/STD/AWOL” [*sic*]. For the benefit of the reader, VDRL refers to Venereal Disease Research Laboratory – a test for syphilis; STD refers to sexually transmitted disease; AWOL signifies away without leave. We believe the commenter is referencing Josef Mengele, a notorious German physician noted for performing cruel experiments on concentration camp prisoners. These issues create doubt about the evidentiary weight that may reasonably be assigned to certain of the public comments.

Of the 657 comments submitted, 620 (94.4%) supported coverage of on label autologous cellular immunotherapy treatment for patients with prostate cancer. Eleven (1.7%) comments submitted were not in favor of Medicare coverage, and an additional 26 (4%) comments did not state support or lack of support of coverage. Eleven (1.7%) commenters addressed research inadequacies and clinical trial design issues related to autologous cellular immunotherapy treatment evaluation.

Seventeen (2.6%) comments cited published evidence related to autologous cellular immunotherapy treatment. We reviewed all referenced literature submitted by commenters.

VIII. CMS Analysis

A. Introduction

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury of to improve the functioning of a malformed body member." See § 1862(a) (1) (A) of the Act.

In addition to section 1862(a)(1)(A), a second statutory provision may permit Medicare payment for items and services in some circumstances. That statute, section 1862(a)(1)(E), provides, in pertinent part, that:

(a) Notwithstanding any other provision of this title, no payment may be made under part A or part B for any expenses incurred for items or services—

. . .

(E) in the case of research conducted pursuant to section 1142, which is not reasonable and necessary to carry out the purposes of that section[.]

. . .

Section 1142 describes the authority of the AHRQ.

Under the authority of § 1862(a)(1)(E), Medicare may cover under coverage with evidence development (CED)/coverage with study participation (CSP) certain items or services for which the evidence is not adequate to support coverage under §1862(a)(1)(A), and where additional data gathered in the context of clinical care would further clarify the impact of these items and services on the health of Medicare beneficiaries. CMS has described CED in greater detail in a guidance document available at http://www.cms.gov/medicare-coverage-database/details/medicare-coverage-document-details.aspx?MCDId=8&McdName=National+Coverage+Determinations+with+Data+Collection+as+a+Condition+of+Coverage%3a+Coverage+with+Evidence+Development&mcdtypename=Guidance+Documents&MCDIndexType=1&bc=BAAIAAAAAAAA&. CED allows CMS to provide coverage based on a determination that an item or service is only reasonable and necessary when it is provided within a research setting where there are added safety, patient protections, monitoring, and clinical expertise.

Under section 1142, research may be conducted on the outcomes, effectiveness, and appropriateness of health care services and procedures to identify the manner in which diseases, disorders, and other health conditions can be prevented, diagnosed, treated, and managed clinically.

For some items or services, CMS may determine that the evidence is preliminary and the item or service is not reasonable and necessary for Medicare coverage under section 1862(a)(1)(A), but, if the following criteria are met CED might be appropriate:

•The evidence includes assurance of basic safety;

•The item or service has a high potential to provide significant benefit to Medicare beneficiaries; and

•There are significant barriers to conducting clinical trials.

These research studies will be rigorously designed and include additional protections and safety measures for beneficiaries.

Questions:

For this analysis for coverage of Sipuleucel-T (PROVENGE®), CMS focused on the following questions:

a. *Is the evidence sufficient to conclude that autologous cellular immunotherapy treatment of metastatic prostate cancer in men whose disease is castration-resistant and who are asymptomatic or minimally symptomatic improves health outcomes of Medicare beneficiaries?*

b. Is the evidence sufficient to conclude that autologous cellular immunotherapy treatment of prostate cancer in men that is either metastatic or not metastatic and whose disease is not castration-resistant and/or who are more than minimally symptomatic improves health outcomes of Medicare beneficiaries?

Question "a" refers to on label use. Question "b" refers to uses that are off label.

Clinical trials in cancer often report a variety of outcomes that differ in their persuasiveness as evidence. As we have stated in other NCD memoranda and in Appendix A of this document,

> CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses.

Thus in reviewing the evidence for this proposed decision we were particularly attentive to reports of changes in those outcomes experienced by patients. In this instance, as we described in the MEDCAC questions, “the health outcomes of interest are: overall survival, control of disease-related symptoms, and the avoidance or minimization of the burdens to patients associated with anticancer therapy.”

<u>1862(a)(1)(A) Analysis</u>

On label Use

Of all of the men who have metastatic, castration-resistant prostate cancer, only a subset are asymptomatic or minimally symptomatic and thus meet the definition for on-label use.

For the on label use of sipuleucel-T (PROVENGE®) the results of two Phase 3 randomized, controlled clinical trials (Kantoff, et al.; Small, et al.) demonstrated improved overall survival in men with metastatic, castration-resistant prostate cancer who were asymptomatic or minimally symptomatic. 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. The resultant statistically significant increase in the overall survival of the patients who received sipuleucel-T compared to those patients who received an active control in these two clinical trials supports the clinical utility of sipuleucel-T in this specific patient population. The pivotal Phase 3 trial (Kantoff, et al.) had an extensive list of clinical criteria to select patients for enrollment in the study, which are listed in Appendix D. The labeled indication was based on the evaluation of the efficacy and safety data obtained in the clinical trial using the clinical criteria as presented in the study protocol

The MEDCAC voting indicated an intermediate degree of confidence among the panelists for the evidence regarding improved health outcomes arising from on label use. This is also consistent with the conclusions of the TA commissioned from AHRQ.

Though the evidentiary weight of certain public comments as evidence is limited by the nature of many of the submissions as we noted earlier, we are mindful that many of the public comments asked for coverage for on label use.

CMS considers whether the evidence base is generalizable to the Medicare beneficiary population. As noted in the Background section, adenocarcinoma of prostate is a disease of older men. As expected, the reviewed clinical trials are well representative of older men. For these reasons, CMS proposes that the evidence is adequate to conclude that sipuleucel-T is reasonable and necessary under section 1862(a)(1)(A) when used on-label.

Health Disparities

We also note that men belonging to minority groups though present were underrepresented as enrolled subjects in the reviewed clinical trials. The Agency for Healthcare Research and Quality (AHRQ) includes the following information on its website at http://www.ahrq.gov/news/nn/nn092910.htm in a release dated September 29, 2010:

- Compared with White men, Black men were still more than twice as likely to die from prostate cancer in 2006, just as they were in 1999 (69 to 50.5 deaths and 29 deaths to 22 deaths per 100,000 males during the period).
- The rate for Hispanics and American Indians/Alaska Natives declined from 23 to 18 and from 17 to 14, respectively per 100,000 males.
- The rate for Asians and Pacific islanders decreased from 14 to 10 deaths per 100,000.

While the disparate death rates may eventually prove to be caused by many factors, we encourage researchers to take appropriate steps to assure that clinical trials enroll subject populations that reflect the distribution of patients affected by the disease.

Off label Use

CMS did not find any evidence from Phase 3 clinical trials designed to evaluate the health outcomes associated with the administration of sipuleucel-T for off label uses. In addition, the TA conclusions and the results of the MEDCAC voting do not support off label use. As the manufacturer acknowledged in the MEDCAC presentation by Mark Frohlich, MD, Dendreon's Chief Medical Officer, "No mature efficacy data supporting off label use of sipuleucel-T." Thus, we do not believe there is any persuasive evidence for the off label use of sipuleucel-T at this time.

While we may nationally noncover items and services that fail to demonstrate achievement of the "reasonable and necessary" statutory requirement, we may also leave it to our local administrative contractors to implement noncoverage. In this case we propose the latter, for the following reasons.

1. The manufacturer has acknowledged at the MEDCAC that there is no persuasive evidence to support unlabeled uses at this time. Thus we are hopeful that unlabeled uses in the near future will take place only in the context of bona fide clinical studies. We may, if this turns out to be an overly optimistic viewpoint, reconsider this NCD to ensure that Medicare coverage is restricted to uses that are supported by robust evidence.

2. Autologous cellular immunotherapy is a new paradigm in the treatment of cancer, and we do not yet know if the development of additional evidence will follow the same trajectory as manufactured pharmaceutical products. Should the pace of evidence development for these products prove to be faster-paced and indicative of improved health outcomes, we believe that preserving local contractors' ability to quickly broaden coverage within their jurisdictions will hasten beneficiary access.

3. The Provenge regimen, in contrast to a manufactured pharmaceutical, is based on the auto-transfusion of the patient's own treated white blood cells. We believe this regimen may evolve over time, whereas with manufactured pharmaceutical products the therapeutic entity itself remains constant. The potency of the administered preparation itself is unique from patient to patient and may even differ in a given patient from administration to administration. If future evidence demonstrates improvement in patient health outcomes as a result of incremental improvement(s) to the current labeled process, we want our administrative contractors to have the flexibility to determine local coverage without the need to reconsider an NCD.

4. Similarly, should future evidence demonstrate improvement in patient health outcomes for populations not meeting the current labeled indication, we want our administrative contractors to have the flexibility to determine local coverage without the need to reconsider an NCD.

1862(a)(1)(E) Analysis

On label Use

Having concluded that the evidence was sufficient to propose coverage under 1862(a)(1)(A) for sipuleucel-T; PROVENGE® for Medicare beneficiaries with asymptomatic or minimally symptomatic metastatic castrate-resistant (hormone refractory) prostate cancer, we do not believe that coverage with evidence development (CED)/coverage with study participation (CSP) is appropriate for that indication.

Off label Use

We next considered whether the evidence was sufficient to propose coverage with evidence development (CED)/coverage with study participation (CSP) for other indications. As has been noted above, the evidence to support such uses is virtually nil at this time. Thus we do not believe that coverage with evidence development (CED)/coverage with study participation (CSP) is appropriate for those indications.

IX. Proposed Decision

The Centers for Medicare and Medicaid Services (CMS) proposes that the evidence is adequate to conclude that the use of autologous cellular immunotherapy treatment - sipuleucel-T; PROVENGE® improves health outcomes for Medicare beneficiaries with asymptomatic or minimally symptomatic metastatic castrate-resistant (hormone refractory) prostate cancer, and thus is reasonable and necessary for that indication under 1862(a)(1)(A) of the Social Security Act (the Act). We are requesting public comments on this proposed determination pursuant to section 1862 (l) of the Act. After considering the public comments, we will make a final determination and issue a final decision memorandum.

APPENDIX A

General Methodological Principles of Study Design

When making NCDs, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

Randomized controlled trials
Non-randomized controlled trials
Prospective cohort studies
Retrospective case control studies
Cross-sectional studies
Surveillance studies (e.g., using registries or surveys)
Consecutive case series
Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

Appendix B

Table 1. Principal Overall Survival Outcomes of RCTs of Sipuleucel-T for the FDA-Approved Indication

Study (ref)	Sample size	Number of deaths by study close-out	Median survival sipuleucel-T group (months)	Median survival placebo group (months)	Hazard ratio (<1 indicates survival in favor of sipuleucel-T)	Confidence interval and p value
IMPACT (11)	Sipuleucel-T (n=341)	210	25.8	21.7	0.78 prespecified adjusted	0.61-0.98, p=0.02
	Placebo (n=171)	121				

Study (ref)	Sample size	Number of deaths by study close-out	Median survival sipuleucel-T group (months)	Median survival placebo group (months)	Hazard ratio (<1 indicates survival in favor of sipuleucel-T)	Confidence interval and p value
D9901 (25)	Sipuleucel-T (n=82)	54**	25.9	21.4	0.59 unadjusted*	0.39-0.88, p=0.01
	Placebo (n=45)	40				
D9902A (10)	Sipuleucel-T (n=65)	44**	19.0	15.7	0.79 unadjusted*	0.48-1.28, p=0.33
	Placebo (n=33)	26				

*Hazard ratio and confidence interval presented is 1/hazard ratio from published source, to be consistent with hazard ratio from IMPACT

**deaths before 36 months

Reproduced in its entirety from Mark et al.

Table 2. Estimated Probability of Survival at 36 Months in RCTs of Sipuleucel-T for the FDA-Approved Indication

Study (ref)	Sipuleucel-T group estimated survival probability (%)	Placebo group estimated survival probability (%)
IMPACT (11)	31.7	23.0
D9901 (25)	34.1	10.7
D9902A (10)	31.6	21.2

Reproduced in its entirety from Mark et al.

Appendix C

Principal Disease Progression Outcomes and Other Secondary Outcomes of RCTs of Sipuleucel-T for the FDA-Approved Indication

Study (ref)	Median time of progression sipuleucel-T group (weeks)	Median time of progression placebo group (weeks)	Hazard ratio	Confidence interval and p value
IMPACT (11)	14.6	14.4	0.95 unadjusted	0.77-1.17, p=0.63
D9901 (25)	11.7	10.0	0.69 unadjusted*	0.47-1.01, p=0.052
D9902A (26)	10.9	9.9	0.92 unadjusted*	0.59-1.45, p=0.72
Pooled D9901 and D9902A (26) Time to pain progression (secondary disease progression analyses)	33.9	32.7	Not reported	0.719
D9901 (26) Time to clinical progression (secondary disease progression analyses)	10.7	9.1	Not reported	0.061

*Hazard ratio and confidence presented is 1/hazard ratio from published source, to be consistent with hazard ratio from IMPACT

Reproduced in its entirety from Mark et al.

Appendix D
The inclusion criteria stated that patients must have:

1. Histologically documented adenocarcinoma of the prostate. The pathology report of a specimen of the primary tumor must confirm prostatic adenocarcinoma and provide the Gleason score.

2. Metastatic prostate cancer as evidenced by soft tissue and/or bony metastases on baseline bone scan and/or computed tomography (CT) scan of the abdomen and pelvis. Patients whose metastatic disease is detectable only on chest CT scan are not eligible.

3. Current or historical evidence of disease progression concomitant with surgical or medical castration, as demonstrated by prostate-specific antigen (PSA) progression OR progression of measurable disease OR progression of non-measurable disease as defined below;
    a. PSA: Two consecutive PSA values, at least 14 weeks apart, each ≥ 5.0 ng/mL and ≥50% above the minimum PSA value observed during castration therapy or above the pre-treatment value if there is no response.
    b. Measurable disease: Soft tissue lesions with clear borders that can be accurately measured on CT or magnetic resonance (MR)[1] with diameters ≥ 2.0 cm. The prostate may not be a site of measurable disease; however, pelvic lesions outside the prostatic fossa may be evaluated as measurable.
    c. Non-measurable disease
        i. i. All other soft tissue lesions, including small lesions (at least 1 diameter < 2.0 cm on CT or MR1), leptomeningeal disease, ascites, pleural or pericardial effusion, lymphangitis cutis/pulmonis, cystic lesions, and cervical nodes. The prostate may not be a site of non-measurable disease; however, pelvic lesions outside the prostatic fossa may be evaluated as non-measurable.
        ii. All bone lesions, as noted on the full body scan. Skeletal events, such as pathologic fracture or skeletal-related spinal cord compression, will be considered non-measurable.
        iii. Soft tissue: The appearance of 1 or more lesions, and/or unequivocal worsening of non-measurable disease when compared to imaging studies acquired during castration therapy or against the pre-castration studies if there was no response.
        iv. Bone disease: Appearance of 2 or more new areas of abnormal uptake on bone scan when compared to imaging studies acquired during castration therapy or against the pre-castration studies if there was no response. Increased uptake of pre-existing lesions on bone scan does not constitute progression.

4. A serum PSA > 5.0 ng/mL at initiation of therapy.

5. Achieved castration levels of testosterone (< 50 ng/dL) via medical or surgical castration. Surgical castration must have occurred at least 3 months prior to initiation of treatment. Patients who are not surgically castrate must be receiving medical castration therapy, have initiated such therapy at least 3 months prior to initiating this treatment, and continue such therapy as clinically warranted.

6. A life expectancy of at least 6 months.

7. Adequate hematologic, renal, and liver function as evidenced by the following:
    a. White blood cell ≥ 2,500 cells/uL
    b. Absolute neutrophil count ≥ 1,000 cells/uL
    c. Platelet Count ≥ 100,000 cells/uL
    d. Hemoglobin ≥ 9.0 cells/dL
    e. Creatinine ≤ 2.0 mg/dL
    f. Total Bilirubin ≤ 2 x upper limit of normal (ULN)
    g. Aspartate aminotransaminase ≤ 2.5 x ULN
    h. Alanine aminotransaminase ≤ 2.5 x ULN

8. Negative serology tests for human immunodeficiency virus 1 and 2, human T cell lymphotropic virus -1, and Hepatitis B and C

In addition, the following exclusion criteria for enrollment in the pivotal clinical trial required that patients must not have:

1. The presence of lung, liver, or known brain metastases, malignant pleural effusions, or malignant ascites.

2. Moderate or severe symptomatic metastatic disease. Subjects who meet either of the following criteria must be excluded:
   a. A requirement for treatment with opioid analgesics for any reason within 21 days prior to enrollment.
   b. Average weekly pain score of 4 or more as reported on the 10-point Visual Analog Scale prior to enrollment.
   c. Eastern Cooperative Oncology Group performance status $\geq$ 2.
   d. Use of non-steroidal antiandrogens (e.g., flutamide, nilutamide, or bicalutamide) within 6 weeks of enrollment.

   Patients who demonstrate an antiandrogen withdrawal response, defined as $\geq$ 25% drop in PSA following discontinuation of a non-steroidal antiandrogen, are not eligible until the PSA rises above the nadir observed after antiandrogen discontinuation. For verification, patients on antiandrogens who are being screened for enrollment in the registry should have a PSA obtained shortly prior to antiandrogen discontinuation. Subsequently, a PSA must be obtained $\geq$ 4 weeks (fluamide) or $\geq$ 6 weeks (bicalutamide, nilutamide) following antiandrogen discontinuation and prior to enrollment.

- Treatment with chemotherapy within 6 months of enrollment except:
  a. When treatment with chemotherapy $\geq$ 3 months of enrollment if all of the following criteria are met:
     i. The post –chemotherapy PSA is $\geq$ the pre-chemotherapy PSA or the nadir PSA achieved during chemotherapy.
     ii. The post-chemotherapy bone scan is not improved in comparison to the pre-chemotherapy bone scan.
     iii. In patients with nodal disease followed by CT or other imaging modality, the post-chemotherapy imaging study must not show a decrease in the size or number of pathologically enlarged lymph nodes in comparison to the pre-chemotherapy imaging study.

- Received more than 2 chemotherapy regimens at any time prior to enrollment.

- Initiation or discontinuation of bisphosphonate therapy within 28 days prior to enrollment.

- Treatment with any of the following medications or interventions within 28 days of enrollment:
  a. Systemic corticosteroids.
  b. External beam radiation therapy or surgery
  c. PC-SPES (or PC-SPEC) or saw palmetto
  d. Megestrol acetate (Megace), diethyl stilbestrol (DES), or cyproterone acetate
  e. Ketoconazole
  f. 5-α-reductase inhibitors (e.g., finasteride [PROSCAR®], dutasteride [AVODART®])
  g. High dose calcitriol [1,25(OH)2VitD] (i.e., > 7.0 ug/week)
  h. Any other systemic therapy for prostate cancer (except for medical castration)

- Treatment with any investigational vaccine within 2 years of enrollment or treatment with any other investigational product within 28 days of enrollment.

- Participation in any previous study involving sipuleucel-T, regardless whether the subject received sipuleucel-T or placebo.

- Pathologic long-bone fractures, imminent pathologic long-bone fracture (cortical erosion on radiography > 50%) or spinal cord compression.

- Paget's disease of bone.

- A history of stage III or greater cancer, excluding prostate cancer. Basal or squamous cell carcinomas must have been adequately treated and the subject must be disease-free at the time of enrollment. Subjects with a history of stage I or II cancer must have been adequately treated and been disease-free for 3 years at the time of enrollment.

- A requirement for systemic immunosuppressive therapy for any reason.

- Any infection requiring parenteral antibiotic therapy or causing fever (temperature >100.5oF or 38.1oC) within 1 week prior to enrollment.

- A known allergy, intolerance, or medical contraindication to receiving the contrast dye required for the CT imaging.

Appendix E Letter from Dendreon to CMS dated February 24, 2011

Dendreon Corporation
3005 First Avenue
Seattle, WA 98121 USA
tel 2062564545
fax 2062560571
www.dendreon.com

February 24, 2011

Louis Jacques, MD
Director, Coverage and Analysis Group
Centers for Medicare and Medicaid Services
Mail Stop S3-02-01
7500 Security Blvd.
Baltimore, MD 21244

Re: Follow up to February 9, 2011 Meeting;
Analyses of Provenge registry to address CMS, MedCAC and AHRQ questions

Dear Dr. Jacques,

In our conversations on February 9, 2011, as well as in the AHRQ technical assessment and the discussions at the MEDCAC meeting, several clinical questions were raised regarding Provenge treatment. I am writing to describe additional analyses we are now planning for our FDA registry that relate to these questions. The scientific advisory board for the registry, comprising clinicians with expertise both in prostate cancer and in the design and analysis of registries, has vetted and approved these analysis plans. The members of the scientific advisory board are listed below. The questions raised at the MEDCAC cover issues of long term follow-up of 'real world' populations, outcomes within subgroups of patients, and the interaction of Provenge with subsequent therapies. Each can be addressed through our analyses of the registry as described below.

The registry will provide information on 1500 individuals treated with Provenge in the setting of routine clinical care. This will produce new insights into the outcomes of patients treated outside of a clinical trial. This group of patients will be larger than the number of patients collectively studied in the Provenge arms of our pre-approval studies. We plan a number of analyses of this cohort, including an assessment of survival overall and cause-specific survival. We anticipate that a large percentage of the subjects in the registry will be enrolled in the Medicare program, as the condition Provenge treats is most prevalent in that age group.

There will be the opportunity in the registry therefore to compare outcomes across age groups, and also to compare the survival of individuals in the registry stratified by age to the outcomes of similar patients in the pivotal studies of Provenge and other publicly available databases. The registry will be of sufficient size to enable analyses of important sub-groups. For example, as you noted in our conversations, and as was discussed during the MEDCAC meeting, the pivotal studies of Provenge, when pooled, demonstrated a large benefit among African-American patients that was substantially greater than that seen among Caucasian patients (HR = 0.288 95% CI = 0.13-0.66). However, the available sample size for this analysis was small (33 African American patients in the treatment arm in the pooled analysis). In the registry we anticipate that between 5% and 10% of treated patients will be African American, which equates to 75 to 150 treated patients. These patients will be followed for both safety and efficacy, allowing for a more stable estimate of survival in this subgroup. The findings will be considered both in comparison to the pooled survival estimate from the pivotal trials in this sub-group, and to the survival of subjects of other races in the registry. Each of these comparisons may lend further insight into the question of whether Provenge is substantially more beneficial in this or any other sub-group than it is in the general population.

The entire treatment course for patients with castrate-resistant prostate cancer is of interest to Dendreon and questions were raised during the MEDCAC meeting about the overall treatment patterns for these patients. In the registry we will catalog the type and timing of therapies that patients receive prior to and subsequent to Provenge, including docetaxel (Taxotere), cabazitaxel (Jevtana), and abiraterone. We will include these treatments as covariates in models of overall survival, allowing us to generate hypotheses about potentially positive or negative interactions between Provenge and such therapies. We plan to disseminate the findings from these and other analyses through meeting abstracts and peerreviewed publications. Please let me know if I can further clarify our plans for this important registry. I appreciate the opportunity to work with CMS to enrich the scientific understanding of Provenge for physicians and patients.

Sincerely,

Mark W. Frohlich, MD
Chief Medical Officer
Dendreon Corporation

Members of Scientific Advisory Board for Dendreon's Registry

Matthew R. Cooperberg, MD, MPH
Assistant Professor, Urology
University of California
San Francisco, CA

Celestia Higano, MD
Professor, Medicine, Division of Oncology & Urology
University of Washington
Seattle, Washington

A. Oliver Sartor, MD
Piltz Endowed Professor of Cancer Research
Professor of Medicine and Urology

Tulane Medical School
New Orleans, LA

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[1] Serial images obtained via MR may be used to evaluate androgen independence prior to initiating the treatment , but may not be used to stage patients or for restaging and assessing disease progression.

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