Technology Assessment

Technology Assessment Program

Outcomes of Sipuleucel-T Therapy

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Outcomes of Sipuleucel-T Therapy

Technology Assessment Report

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Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center

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This report is based on research conducted by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract Number HHSA 290 2007 10058 I). The findings and conclusions in this document are those of the authors who are responsible for its contents. The findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of the Agency for Healthcare Research and Quality or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decision-makers; patients and clinicians, health system leaders, and policymakers, make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment.

Decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Peer Reviewers

We wish to acknowledge individuals listed below for their review of this report. This report has been reviewed in draft form by individuals chosen for their expertise and diverse perspectives. The purpose of the review was to provide candid, objective, and critical comments for consideration by the EPC in preparation of the final report. Synthesis of the scientific literature presented here does not necessarily represent the views of individual reviewers.

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Executive Summary

Background. Sipuleucel-T (Provenge®, Dendreon Corporation) is a recently approved treatment for asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer. This technology assessment is a systematic review of studies of the clinical outcomes of sipuleucel-T treatment. The review is organized by three Key Questions. These questions address the following: 1) the outcomes of sipuleucel-T for patients meeting the U.S. Food and Drug Administration (FDA) -labeled indications; 2) the outcomes of sipuleucel-T for patients not meeting the FDA-labeled indication ("off-label use"); and 3) adverse effects of sipuleucel-T treatment. Key Questions 1 and 2 also include subquestions to address possible interactions and mediators of the outcomes of sipuleucel-T treatment.

Methods. This assessment is based on an electronic search of the literature as follows:

- MEDLINE® (inception [1948] through July 13, 2010)
- EMBASE® (inception [1974] through July 13, 2010)
- Cochrane Controlled Trials Register (no date restriction)

In addition, publicly available documents available from the FDA website and some other sources such as clinicaltrials.gov and conference abstract websites were examined for relevant studies. Studies were selected to address the three Key Questions identified for this technology assessment. We abstracted data from full-length randomized, controlled trials (RCTs) and case series studies that utilized sipuleucel-T treatment for patients with prostate cancer and reported at least one clinically relevant outcome of interest.

The quality of included comparative studies was assessed using the general approach to grading evidence developed by the U.S. Preventive Services Task Force (USPSTF). The strength of the overall body of evidence was assessed using a framework developed by AHRQ for the EPC Methods Guide, based on a system developed by the GRADE Working Group.

Results. The electronic literature search yielded 47 records. Among those, 33 were excluded at initial title and abstract review and 14 were retrieved for full-text examination. Including documents retrieved from other sources, data were available from 10 nonoverlapping data sets. Data from three studies describing results of comparative studies were abstracted for studies examining the FDA-labeled indication. Data from seven studies describing results of any study design were abstracted for studies examining off-label indications. Data from a single analysis of pooled data from four comparative studies were abstracted for the analysis of adverse effects of sipuleucel-T.

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?

Three randomized clinical trials of sipuleucel-T share a common study design which includes control groups that underwent leukapheresis and infusion of untreated cells, availability of a salvage product for the control group upon disease progression, and treatment as needed in either group upon disease progression. Two of the three studies were statistically significant for

survival in favor of sipuleucel-T in unadjusted or prespecified analyses; the third study showed a similar magnitude of effect but was not statistically significant. None of the studies showed a statistically significant difference in disease progression end points. Quality of life outcomes were not assessed. Post-disease progression chemotherapy was a common event for participants in these clinical trials. Analyses undertaken to account for potential confounding effects of these subsequent treatments and other factors produced similar estimates of treatment effect, but such methods may be limited in the ability to fully account for such effects. The strength of the body of evidence for improved outcomes was graded as moderate.

Question 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?

Regarding patient baseline characteristics, there are no conclusive findings regarding potential interactions with sipuleucel-T treatment. One study showed a significant interaction with age at a cutoff of 65 years, but analysis of pooled data showed less extreme results and makes this finding inconclusive. The conclusions to be drawn regarding the association product parameters and survival are limited because it is not possible to separate a treatment effect from an inherent characteristic of the patient. Associations were found with several product parameter measures, but no such analyses are available from such measures done on the control groups of the studies. Post-progression chemotherapy was a common event in these studies, but the existing analysis is insufficient to determine the independence or interaction of sipuleucel-T with such treatment.

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

Outcomes for sipuleucel-T have been reported for patients with metastatic castrate-resistant prostate cancer without specification of symptoms, nonmetastatic castrate-resistant prostate cancer, and nonmetastatic hormone-sensitive prostate cancer. Six sets of findings for off-label indications are all case series studies. The case series studies all differed in the treatment protocol for sipuleucel-T than the protocol currently used. Without a comparison group, it is not possible to determine whether the outcomes observed are attributable to sipuleucel-T. One randomized clinical trial is unpublished, with a conference abstract reporting no significant difference for the principal outcome of biochemical failure. There is insufficient evidence to evaluate the outcomes for off-label indications.

Question 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?

In light of the insufficient evidence for Key Question 2, there is insufficient evidence to evaluate this additional question.

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

A pooled analysis of the three randomized trials for the FDA-labeled indication and one randomized trial for an off-label indication was reviewed. Sipuleucel-T causes events consistent with an infusion reaction, which are rarely severe enough to cause hospitalization. Sipuleucel-T therapy also is associated with catheter-related infections. For other types of adverse effects, the data are inconclusive. FDA is requiring a postmarketing registry to assess the incidence of cerebrovascular events. The data are inconclusive regarding the association of cerebrovascular events and sipuleucel-T treatment. No associations of product parameters or patient characteristics with adverse events were identified.

Conclusions/Future Research Issues. 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 potential for confounding due to a systematic difference in application of effective post-progression treatment, likely to be due to delays caused administration of frozen salvage product. The quantity of benefit of sipuleucel-T is less certain because of these issues. There is little evidence regarding potential interactions with baseline patient characteristics but the current studies are weakly powered to detect such interactions. There is insufficient evidence for any off-label indication.

Future clinical trials of sipuleucel-T should 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 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. Such information is critical for decisions physicians and patients need to make as they plan how to treat the patient's cancer.

INTRODUCTION

The Coverage and Analysis Group at the Centers for Medicare and Medicaid Services (CMS) requested this report from the Technology Assessment Program (TAP) at the Agency for Healthcare Research and Quality (AHRQ). AHRQ assigned this report to the following Evidence-based Practice Center: Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center (Contract Number: HHSA 290 2007 10058 I). The specific questions to be addressed are described at the end of the Introduction.

Epidemiology of Prostate Cancer

Prostate cancer is the most common malignancy in men and a common cause of cancer mortality. The 2010 American Cancer Society estimates for prostate cancer in the U.S. are approximately 217, 730 new cases of prostate cancer and 32,050 prostate cancer deaths.[1] Approximately one man in six will be diagnosed with prostate cancer during his lifetime. More than 2 million men in the U.S. who have been diagnosed with prostate cancer at some point are still alive today.

Initial treatment strategies for localized prostate cancer include active surveillance, radiation therapy, brachytherapy, and surgery.[2] After initial treatment, patients are monitored for recurrence by measuring prostate-specific antigen (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 prostate cancer.

Castrate-Resistant Prostate Cancer

Treatment recommendations for castrate-resistant prostate cancer according to the most current National Comprehensive Cancer Network (NCCN) guidelines, depend on whether metastatic disease is present or not.[2] In the absence of metastases, observation, enrollment in a clinical trial, antiandrogen withdrawal, or secondary ADT are among the mentioned options. In the presence of metastases, sipuleucel-T (Provenge®, Dendreon Corporation), docetaxel (Taxotere®, Sanofi Aventis) chemotherapy, mitoxantrone (Novantrone®, Serono Laboratories) and corticosteroids, secondary ADT, and palliative radiation therapy for symptomatic bone metastases are the listed options. Secondary ADT is commonly used prior to consideration for chemotherapy. Docetaxel has been demonstrated to prolong survival in randomized clinical trials.

However, even with treatment, the prognosis of castrate-resistant prostate cancer is not very good, with median survival generally less than two years. Various characteristics of patients have been correlated with survival in several studies. According to a prognostic model developed by Halabi and co-workers, longer survival was predicted by a Gleason score less than 8, better performance status, lower levels of baseline PSA, lactate dehydrogenase (LDH), and

alkaline phosphatase, a higher hemoglobin level, and absence of visceral disease.[3] In this study sample, largely drawn from clinical trials before docetaxel chemotherapy was used in patients with prostate cancer, the lowest to highest predicted risk quartiles had actual median survivals of 7.5, 13.4, 18.9, and 27.2 months, respectively. In another prognostic model by Smaletz and colleagues, longer survival was associated with better performance status, lower levels of alkaline phosphatase and LDH, and higher levels of hemoglobin and albumin.[4] PSA levels and age were not associated with survival, but were included in the prognostic model. Finally, in a prognostic model based on the clinical trial that led to U.S. Food and Drug Administration (FDA) approval of docetaxel for castrate-resistant prostate cancer, in addition to all the variables included in the predictive model of Halabi et al., longer survival was associated with absence of pain at baseline, fewer metastatic sites, longer PSA doubling time, and PSA-only type of progression (versus measurable disease or bone scan progression).[5]

Prior to the approval of sipuleucel-T, the only treatment demonstrated to have improved survival of castrate-resistant prostate cancer in randomized clinical trials was docetaxel. In the clinical trial that led to FDA approval for this indication, 1,006 men were randomly assigned to either mitoxantrone plus prednisone or 2 different regimens of docetaxel plus prednisone (i.e., every 3 weeks or every week).[6] The comparator regimen in this study, mitoxantrone, had previously been demonstrated to have palliative effects for prostate cancer symptoms, but had not demonstrated improvement in survival. Compared with mitoxantrone, the group given docetaxel every 3 weeks had a hazard ratio for death of 0.76 (95 percent confidence interval [CI]: 0.62–0.94). The median survival was 16.5 months in the mitoxantrone group compared to 18.9 months in the group given docetaxel every 3 weeks, a difference of 2.4 months. The group given docetaxel every 3 weeks also had greater reductions in pain and greater percent improvement in measures of quality of life. The group given weekly docetaxel generally had outcomes intermediate between the other two groups, with some of the outcomes not being statistically significantly different than the mitoxantrone group. An updated survival analysis of this trial shows similar results; the group given docetaxel every 3 weeks has a median survival of 19.2 months, versus 16.3 months in the mitoxantrone group.[7]

In another study by Petrylak and colleagues, 770 men were randomized to either estramustine plus docetaxel every 3 weeks or mitoxantrone plus prednisone every 3 weeks.[8] The overall median survival was 15.6 months in the mitoxantrone group and 17.5 months in the docetaxel group (p=0.02), a difference of 1.9 months, and the corresponding hazard ratio for death was 0.80 (95 percent CI: 0.67–0.97).

Like many chemotherapy agents, docetaxel has several adverse effects, the most common ones being hair loss, nausea and vomiting, fatigue, sensory neuropathy, and neutropenia. In the FDA pivotal trial, these particular events all occurred at a frequency of 30 percent or greater in the group given docetaxel every 3 weeks.

Although docetaxel is approved for castrate-resistant prostate cancer as is sipuleucel-T, their labeled indications are not identical. One major difference is that the patients must not necessarily be asymptomatic or minimally symptomatic. The clinical trials of docetaxel enrolled a high proportion of patients with baseline pain (45 percent with a minimum score or 2 or more on the Present Pain Intensity Scale in the FDA pivotal trial, 36 percent in the trial of Petrylak et al.[8]). The results of the FDA pivotal trial stratified by baseline pain appear to produce qualitatively similar relative amounts of benefit in both patients with and without pain. Some investigators believe this causes many practitioners to defer docetaxel therapy until symptoms develop or there is a rapid rise in PSA levels, in order to balance the benefit of therapy with the

desire to defer toxicity.[9] The NCCN guidelines do not address the issue of the timing of chemotherapy. Some articles have suggested that because of the longer survival of pain-free patients relative to patients with baseline pain, the benefit of docetaxel in pain-free patients may translate to a longer survival benefit, and thus consideration should be given to giving docetaxel before symptoms develop.[9]

Sipuleucel-T

The biologic premise of sipuleucel-T is that the treatment stimulates the patient's own immune system to target prostate cancer cells. T-cells that are sensitized to specific antigens present on prostate cancer cells may be able to destroy or prevent proliferation of cancer cells.

Sipuleucel-T is manufactured from the patient's own white cells, which are collected from a procedure called leukapheresis.[10] The leukapheresis procedure essentially filters out the cells of interest and retransfuses the remainder back into the patient. The collected cells, which are mixture of peripheral blood mononuclear cells including antigen-presenting cells, T-cells,, and B-cells, are then cultured with a protein called PA2024. PA2024 is a recombinant protein consisting of human prostatic acid phosphatase (PAP) fused with granulocyte-macrophage colony stimulating factor (GM-CSF). The interaction of the antigen-presenting cells with PA2024 is considered the essential process that stimulates the immune system. Antigen-presenting cells take in antigens and then "present" them to T-cells throughout the body, which should then react to cells with PAP such as prostate cancer cells as foreign substances. The entire process from leukapheresis to infusion of sipuleucel-T is approximately 3 days. Sipuleucel-T must be administered within 18 hours of manufacture. The dosing regimen for the FDA-labeled indication is 3 doses, each 2 weeks apart, for a total treatment period of 4 weeks.

Because sipuleucel-T is made from a patient's own white cells, particular aspects about the treatment should be noted. The cellular composition of each dose is dependent on the composition of cells obtained during leukapheresis, which can vary between patients and in a single patient between leukapheresis sessions. According to the published report of the pivotal FDA trial of sipuleucel-T, each dose contained a minimum of 40 million cells expressing the co-stimulatory molecule CD54.[11] Cells expressing CD54 are considered the active ingredient of the treatment. However, the variation between doses in the number of cells expressing CD54 may be great. In an early study of sipuleucel-T by Small and colleagues, although the current manufacturing process may vary from that study, the median number of CD54 cells in each dose was 278 million cells, with a range between 18.6 and 1,276 million, more than a 50-fold difference.[12] The minimum cell requirements for a satisfactory dose of sipuleucel-T may require the patient to undergo additional leukapheresis procedures.

Immunologic Response to Sipuleucel-T Treatment

In the studies of sipuleucel-T to be reported later in this technology assessment, various types of immunologic tests were performed on the cells of patients treated with sipuleucel-T.[12–14] The types of findings observed will be summarized in this section of the technology assessment, as they relate to the possible mechanisms and biology of the treatment, and are not themselves clinical outcomes. Some of these observations may provide clinical value as predictors of treatment success or patient prognosis.

T-cells of patients who have been treated with sipuleucel-T will replicate when exposed to PA2024, PAP, and GM-CSF. A T-cell proliferation assay can measure the degree to which T-cells will replicate in response to exposure to specific types of antigens, which is considered a measure of successful induction of immunity to that particular substance. All the human studies of sipuleucel-T have demonstrated that there is a greater proliferation of T-cells in response to PA2024, PAP, and GM-CSF after treatment than before treatment. Such studies have also tested proliferation to control substances and to common influenza antigens, and demonstrated that the T-cell proliferation response to these antigens is explained by exposure to sipuleucel-T. Antibodies to PA2024, PAP, and GM-CSF can be detected in a greater proportion of patients after treatment than before treatment, as well.

A process that has been proposed as a measure of the potency of sipuleucel-T is called CD54 upregulation.[10] During the manufacture of sipuleucel-T, the number of CD54 molecules expressed on the antigen-presenting cells increases. The amount of this increase can be quantified using specific assays. The quantity of this increase varies between patients, and varies depending on prior exposure to sipuleucel-T. Greater CD54 upregulation is observed after the first dose of treatment, indicating that antigen-presenting cells respond differently to culture in PA2024 after an initial systemic exposure to sipuleucel-T. The potential role of CD54 upregulation as a predictor of patient response will be discussed more thoroughly in a later section of this technology assessment.

U.S. Food and Drug Administration (FDA) Approval and Prescribing Information

In April 2010, sipuleucel-T was approved by the FDA. The indication approved was for the treatment of asymptomatic or minimally symptomatic castrate-resistant (hormone-refractory) prostate cancer. There is some notable information in the full prescribing information document that will not be covered in this technology assessment, but should be mentioned because this information will probably affect the clinical use of sipuleucel-T.[15] Most notably, there are no contraindications listed. Warnings and precautions are stated regarding the possibility of acute infusion reactions, the risk of transmissible infectious disease to health care professionals handling the product, and that the prior, concomitant, and post-treatment use of chemotherapy and immunosuppressive medications has not been studied. It is additionally stated that the concurrent use of immunosuppressive agents may alter the efficacy and/or safety of sipuleucel-T, and that "patients should be carefully evaluated to determine whether it is appropriate to reduce or discontinue immunosuppressive agents prior to treatment…"

Practice Guidelines

Sipuleucel-T is included as a category I recommended treatment for patients meeting the FDA-labeled indication in the most recent version of the NCCN practice guidelines for prostate cancer.[2] The guideline mentions that the treatment is only recommended for patients who have good performance level, estimated life expectancy greater than 6 months, no visceral disease, and no or minimal symptoms. The guideline notes that markers of benefit of therapy are usually not seen and the benefit to the individual patient cannot be currently ascertained.

Key Questions to be Addressed by this Technology Assessment

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?

Question 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?

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

Question 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?

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

METHODS

As detailed below, certain aspects of Methods and Materials may vary to satisfy requirements of each question. However, the Methods are generally applicable to all Key Questions, including Methods of the Review, Evidence Tables, Identifying Additional Studies, and Assessing Study Quality.

Database Search Strategies

The following electronic databases were searched for citations (search strategy can be found in Appendix C).

- MEDLINE® (inception [1948] through July 13, 2010)
- EMBASE® (inception [1974] through July 13, 2010)
- Cochrane Controlled Trials Register (no date restriction)

The search was limited to English-language references. Because the review of on-label uses primarily focused on randomized, controlled trials (RCTs), the Cochrane Handbook search strategy for controlled trials was applied.[16]

The searches resulted in 47 unique citations. In addition to the electronic database searches, we examined the bibliographies of all retrieved articles for citations to any RCT or case series that was missed in the database searches. We searched clinicaltrials.gov and fda.gov for information on any clinical trials of sipuleucel-T. We performed online searches of selected conference proceedings and abstracts.

Patient Populations

The populations of interest are definable categories of patients with prostate cancer for which sipuleucel-T has been used to treat prostate cancer. The FDA-labeled indication for sipuleucel-T is patients with asymptomatic or minimally symptomatic patients with castrate-resistant (hormone-refractory) prostate cancer.

Off-label indications can only be surmised by the particular inclusion and exclusion criteria of the particular studies we have reviewed. Some early studies of sipuleucel-T included patients similar to the FDA-labeled indication, but without the requirement of no or minimal symptoms. However, based on the high Eastern Cooperative Oncology Group (ECOG) performance scores reported for these patients, they appear to be very similar to patients meeting FDA-labeled indications.

Other groups of patients enrolled in studies that could be said to describe an indication for use of sipuleucel-T include patients with progressive nonmetastatic castrate-resistant prostate cancer and patients with recurrent nonmetastatic hormone-sensitive prostate cancer. The former group represents a generally earlier time in the sequence of cancer progression than the FDA-labeled indication. The latter group represents the earliest time of cancer recurrence after failure of primary treatment.

Interventions

The intervention of interest for all key questions is the use of sipuleucel-T for the treatment of prostate cancer. In the randomized trials of sipuleucel-T, no other treatment was given until disease progression. At that point in time, patients were then treated at the discretion of their own physician. Thus, these trials represent a treatment strategy of sipuleucel-T and deferral of other treatment until disease progression, then as indicated in the judgment of the treating physician.

Comparators

Comparators are the standard treatment for patients with prostate cancer at the particular stage of disease or indication at which sipuleucel-T was administered in the studies. For the RCTs, the comparator treatment strategy is explicit. Placebo sipuleucel-T infusions, which consist of infusion of untreated autologous cells, followed by observation until disease progression represent a strategy of watchful waiting and deferred treatment, at least until objective disease progression, then additional treatment at the discretion of the patient and physician.

For the case series studies, the implied comparator is watchful waiting. For the patient indications for which sipuleucel-T has been given, this is a reasonable comparator, although active treatment is an option.

Outcomes of Interest

Benefits

Outcomes of interest include overall survival, quality of life, and cancer progression. Because of the novel nature of this treatment, it is not known if commonly used surrogate measures of outcome in prostate cancer such as change in PSA levels or change in PSA doubling time correlate with more definitive outcome measures. The validity of such surrogate measures in the context of sipuleucel-T treatment would need to be established in prospective studies. Measures of immunologic function or immunologic reaction to sipuleucel-T are physiologic tests, not health outcomes, and we did not routinely abstract these data as a relevant health outcome.

Harms

Adverse effects occurring during or after treatment may be attributable to sipuleucel-T based on biologic plausibility, temporal association to sipuleucel-T administration, or a formal comparison of potentially attributable events in the treated group compared to a control group followed with equal intensity for the adverse events.

Study Selection Criteria

Studies were selected to address the Key Questions identified for this technology assessment. One reviewer screened titles and abstracts of identified studies using the following eligibility

criteria. If this could not be done satisfactorily from the title and abstract, we obtained a full-text version for assessment. Articles published in a language other than English were not included in this technology assessment.

Key Question 1

We abstracted data from case series and randomized clinical trials that utilized sipuleucel-T therapy in patients meeting the FDA-approved indication that measured a health outcome of interest.

Key Question 2

We abstracted data from any type of study enrolling a series of patients that utilized sipuleucel-T therapy for a definable indication of patients with prostate cancer, not meeting the FDA-approved indication that measured a health outcome of interest.

Key Question 3

We originally planned to abstract data from any type of study enrolling a series of patients that reported the incidence of adverse effects in patients undergoing treatment with sipuleucel-T, including studies where analyses attempted to determine associations and causation of the adverse effects. However, most case series studies used treatment protocols different than the current FDA-labeled indication, and the preparation of sipuleucel-T may have varied from the current product.

To summarize the information with the largest data set using current treatment protocols, we abstracted data from the FDA Clinical Review of sipuleucel-T.[17] This Clinical Review pooled data from all four RCTs that have investigated the treatment. Adverse effects were assessed in very close to uniform methods across all four studies using established methods for measuring adverse effects.

Data Analysis and Presentation

Electronic search results were stored in a ProCite® database and the number of references retrieved and included in the technology assessment was documented. Using the final study selection criteria for screening titles and abstracts, a single reviewer marked each citation as 1) eligible for review as a full-text article, 2) ineligible for full-text review.

Detailed records of the results of this evaluation were kept for each paper retrieved in full text, including the reason for exclusion of each excluded study. The following data elements of primary studies were abstracted as available from the articles meeting all selection criteria.

a. General information: title, authors, source, year of publication, duplicate publications, setting, funding
b. Trial characteristics: method of randomization, concealment of allocation, blinding of patients and clinicians

c. Patients: sampling, exclusion criteria, sample size, baseline characteristics, similarity of groups at baseline, diagnostic criteria, withdrawals, losses to follow up
d. Interventions: dose, dosing regimen, duration, route, co-medications with dose, timing
e. Analytical methods
f. Outcomes: outcomes as specified above

Evidence Tables

We created templates for evidence tables in Microsoft Word®. One reviewer performed primary data abstraction of all data elements into the evidence tables, and a second reviewer performed accuracy checks on the evidence tables.

Assessment of Study Quality

The quality (internal validity) of included studies (RCTs and other comparative designs) was assessed on the basis of the general approach to grading evidence developed by the U.S. Preventive Services Task Force.[18] Quality criteria were as follows:

a. Initial assembly of comparable groups: adequate randomization, including concealment and whether potential confounders (e.g., other concomitant care) were distributed equally among groups
b. Maintenance of comparable groups (includes attrition, crossovers, adherence contamination)
c. Important differential loss to follow-up or overall high loss to follow-up
d. Measurements: equal, reliable, and valid (includes masking of outcome assessment)
e. Clear definition of interventions
f. All important outcomes considered
g. Analysis: adjustment for potential confounders, intention-to-treat analysis
h. The rating of intervention studies encompasses the three quality categories described here:

Studies were rated as "good" if they met all criteria: Comparable groups were assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments were used and applied equally to the groups; interventions were spelled out clearly; all important outcomes are considered; and appropriate attention was given to confounders in analysis. In addition, for RCTs, intention-to-treat analysis was used.

Studies were rated as "fair" if any or all of the following problems occurred, without the fatal flaws noted in the "poor" category below: In general, comparable groups were assembled initially but some question remained as to whether some (although not major) differences occurred with follow-up; measurement instruments were acceptable (although not the best) and generally applied equally; some but not all important outcomes were considered; and some but not all potential confounders were accounted for. In addition, for RCTs, intention-to-treat analysis was used.

Studies were graded "poor" if any of the following fatal flaws existed: Groups assembled initially were not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments was used or not applied at all equally among groups (including not masking outcome assessment); and key confounders were given little or no attention. For RCTs, intention-to-treat analysis was lacking.

For studies of adverse effects, there are no validated standard tools to assess either reporting bias or completeness for harms. Consequently, reporting was assessed using an empirically derived set of questions informed by the McMaster Quality Assessment Scale for Harms (McHarm) and the Agency for Healthcare Research and Quality (AHRQ) draft Methods Manual guidance.[19,20]

- Is there an explanation of how harms were identified?
- Was a standardized or validated instrument or scale used?
- Was ascertainment similar and complete in all study groups?
- Was a measure of severity reported?
- Were harms attributed to the study intervention likely causally associated?
- Were the number and type of harmful events reported separately for study groups?

Data Synthesis

This evidence review did not incorporate quantitative data synthesis using meta-analysis. Studies for the same indication are presented and discussed together, and evaluated on the basis of individual study quality for potential biases and errors. Consistency of the findings is evaluated qualitatively.

Rating the Body of Evidence

The system used for rating the strength of the overall body of evidence was developed by AHRQ for the EPC Methods Guide, based on a system developed by the GRADE Working Group.[21,22] This system explicitly addresses the following domains: risk of bias, consistency, directness and precision. Grade of evidence strength was classified into the following four categories:

- High: High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate: Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- Low: Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
- Insufficient: Evidence is either unavailable or does not permit estimation of an effect.

RESULTS

Search Results

The electronic literature search yielded 47 unique records, of which 33 were excluded at initial title and abstract review and 14 were retrieved for full-text examination. Based on the study selection criteria, 6 articles met inclusion criteria. However, the electronic search did not include publications available from the FDA. Subsequent to the search, one RCT was published.[11] Search of a bibliography of a review article revealed one additional article that met entry criteria.[13] We decided to include an unpublished RCT in which results are published in a conference abstract.[23] One publication reported pooled findings of two studies.[24] One published study reported results for two indications for use of sipuleucel-T.[12] Review of conference abstracts revealed pooled analyses of previously identified clinical trials.[25–28] Due to lack of sufficient information and data presentation in these abstracts, we did not include them in this review.

Therefore, it is most clear to report search results in terms of the number of independent patient data sets found, rather than the number of publications. For Key Question 1, there are three independent data sets reported in three peer-reviewed publications and several documents available from the FDA website.[11,17,24,29–33] For Key Question 2, there are seven sets of findings from five peer-reviewed publications and a conference abstract.[12–14,23,34–36] For Key Question 3, we relied on one set of pooled findings from an FDA clinical review.[17]

Synthesis of Evidence for Key Questions

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?

Evidence regarding this question consists of three RCTs, published in various documents and to greater or lesser depth in numerous forms.[10,11,17,24,29–33] To identify the studies consistently, we designate the studies as "IMPACT," "D9901," and "D9902A," throughout this technology assessment, regardless of the source of the information.

Abstraction of key results for this technology assessment was complicated by the multiple sources. These sources included peer-reviewed journal publications, FDA-authored clinical reviews, FDA-authored statistical reviews, and company-authored briefing documents prepared for FDA committee meetings.

At least two issues arise from this quantity of published materials regarding the performance of this technology assessment. One issue is a problem with potentially 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.

Another issue is 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.

Rather than attempt to abstract all these analyses, we decided to try to characterize and summarize these analyses in brief form in Appendix A. The tables accompanying the text within this document will focus on what we consider to be the principal results of the studies.

Finally, 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.

The D9901 and D9902A study results were pooled for analysis in a peer-reviewed publication and in publications prepared for the FDA.[10,24] Several conference abstracts consisted of analyses of pooled data.[25–28] We will not routinely present these pooled analyses because the pooled analyses do not really represent additional independent evidence. Certain analyses appear to be only available from these pooled analyses, and we will present as necessary.

Study Design of IMPACT, D9901, and D9902A

All three studies had very similar structure, except for minor variations in entry criteria and nonsurvival outcome measures. Patients were randomized 2:1 to either sipuleucel-T or placebo. Patients had leukapheresis and infusion at weeks 0, 2, and 4, and then were followed for study end points. Placebo patients underwent identical leukapheresis at the same intervals, but received infusions of about one-third of their untreated cells back as placebo. The remaining two-thirds of their cells were cryopreserved. After disease progression occurred in the placebo group, they were offered the opportunity to receive a salvage product consisting of their own cells, which were then thawed and prepared in a similar method as sipuleucel-T. 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. Upon disease progression in both groups, patients could be treated at the discretion of their own treating physicians.

The design of the study raises some issues regarding internal validity. First, the leukapheresis and placebo infusion is not a truly inert placebo. Complications could occur, and this should be considered in understanding the adverse effects of sipuleucel-T. Second, effects either positive or negative of frozen salvage product could affect the validity of the study. In many randomized studies therapies, patients are often offered to "cross over" to active treatment.

If the cross-over treatment has a treatment effect in the same direction as the original treatment, then in most cases a conservative bias would result, so that the usual intention-to-treat analysis of the trial would result in a conservative estimate of treatment effect. Third, treatment administered after disease progression could potentially confound the results if the provision of effective treatments varies between the active and placebo-treated groups.

Patients

The principal entry criterion for the studies was metastatic castrate-resistant prostate cancer. Studies D9901 and D9902A enrolled asymptomatic patients, IMPACT enrolled asymptomatic and minimally symptomatic patients (Appendix Table A1). "Minimally symptomatic" was defined as not requiring opioid analgesics within 21 days of registration, and an average weekly pain score of less than 4 on a 10-point visual analog scale on the registration pain log. Other aspects of the selection criteria are specifically stated in various protocol documents, but can be characterized as selection of patients in reasonably good health (e.g., good ECOG performance scores, expected survival of at least 6 months), without signs of prognostically poor disease (i.e., without visceral metastases, long bone fractures, or spinal cord progression), reasonably distant in time from prior chemotherapy (various criteria for recency of prior therapy), and normal immunologic function (various laboratory and serology values).[30,37]

The entry criteria Gleason score for IMPACT was changed during the trial from 7 or less to any Gleason score. Thus, compared to D9901 and D9902A, IMPACT enrolled a higher proportion of subjects with Gleason scores of 7 or less.

Outcomes

All trials reported overall survival. However, studies D9901 and D9902A were designed for an end point of progression-free survival, and the primary end point of IMPACT was changed from progression-free survival to overall survival. The design of the studies reflects the emphasis on the original progression end point, with rigorous efforts to blind patients and investigators and objective criteria to determine progression. After progression, there were fewer guidelines regarding patient management.

The progression end point varied slightly between each of the studies, but largely involved evaluation of lesions observed on serial bone scans and computed tomography. IMPACT considered only imaging results in the assessment of disease progression; D9901 and D9902A considered imaging and certain clinical events such as lesion-associated onset of pain as progression events.

Quality of life was not specifically assessed in any of the studies. The protocols for studies D9901 and D9902A include secondary end points of time to onset of disease-related pain and time to clinical progression.

Adverse events were collected using standard methods up to 16 weeks (in D9901 and D9902A) or until disease progression (in IMPACT). After this interval, adverse events with the exception of cerebrovascular events were only collected if it was determined by the investigators to be possibly related to sipuleucel-T treatment. Causes of death were apparently collected and analyzed, but there is no description in any protocol documents regarding an algorithm for determining cause of death or an adjudication process. Descriptions of some case reports in

documents reveal that death certificate data was used as the source of information for cause of death for at least some subjects.

Results of IMPACT, D9901, D9902A

IMPACT enrolled 512 patients, D9901 enrolled 127 patients, and D9902A enrolled 98 patients. In terms of the quality rating of the studies, in many attributes the studies are good quality. In terms of the original disease progression end point, the studies would overall be good quality. However, because of potential confounding effects occurring after disease progression, they received a fair rating for the study end point of survival (Appendix Table A2).

Baseline characteristics appear to be reasonably balanced between sipuleucel-T and placebo groups in all the studies. Although IMPACT enrolled patients with minimal symptoms and the other trials only enrolled asymptomatic patients, the mean ECOG performance scores of patients enrolled in IMPACT equal or surpass those of patients in the other trials. The original strict Gleason score criteria of the IMPACT trial resulted in a higher proportion of patients with more favorable Gleason scores. Also notable among the baseline characteristics is that 18 percent of subjects in IMPACT had undergone prior chemotherapy, whereas lower proportions of subjects in D9901 and D9902A had undergone chemotherapy. This might be due to the slightly different exclusion criteria regarding history of prior chemotherapy. There do not appear to be outstanding differences in other patient characteristics and disease status between IMPACT, D9901, and D9902A.

Overall survival outcomes of all three trials are shown in Table 1. All studies followed patient survival end points until over 67 percent of patients had died. In all three studies, the median survival of the sipuleucel-T groups was greater than the survival of the placebo groups. The difference in median survival between groups was 4.1 months in IMPACT, 4.5 months in D9901, and 3.3 months in D9902A. However, 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. The same results expressed as survival probability at 36 months after randomization are shown in Table 2. Issues regarding variations and alternative formulations of these survival analyses are discussed in Appendix Table A3. We did not feel these alternative analyses particularly strengthened or weakened these principal overall survival results.

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=0.03
	Placebo (n=171)	121				
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

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

The principal disease progression end points for each of the studies are shown in Table 3. The hazard ratio for progression was 0.95 in IMPACT, 0.69 in D9901, and 0.92 in D9902A. None of these hazard ratios met a 0.05 level of statistical significance. The difference in median time to progression was 0.2 weeks in IMPACT, 1.7 weeks in D9901, and 1.0 weeks in D9902A.

A pooled analysis of D9901 and D9902A was performed for a secondary end point of time to pain progression. However, this analysis is limited by censoring; patients only completed a pain and analgesic log 4 weeks beyond the time of disease progression. This resulted in almost two-thirds of patients being censored because there were no pain events within 4 weeks after disease progression. Nonetheless, 79 pain events consistent with cancer progression occurred in 225 patients. Median time to pain progression was 33.9 weeks for sipuleucel-T subjects and 32.7 weeks for placebo subjects, which was not statistically significant (p=0.719). An analysis of time to clinical progression of subjects in D9901, basically a slight variation of the principal disease progression analysis, showed no difference in median time to clinical progression.

Consideration of Post-Progression Treatments

After progression, a high proportion of subjects in the placebo groups received frozen salvage product; 63.7 percent in IMPACT, 75.6 percent in D9901 and 66.7 percent in D9902A (Table 4). In IMPACT, the median survival for subjects receiving frozen salvage product was 23.8 months and 11.6 months for those who did not. 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 Any simple comparison of survival of two groups in which group membership is defined by events occurring after baseline will be biased. Such a survival bias cannot be removed by adjustment for patient characteristics.

Some patients in both groups received subsequent chemotherapy treatments after progression, including docetaxel chemotherapy, which has been demonstrated to have a survival benefit in RCTs. The proportion of patients receiving docetaxel chemotherapy in each trial is shown in Table 4. In IMPACT, 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.

Analyses were presented to attempt to adjust for these potential confounding effects of subsequent docetaxel treatment. Results of these analyses are shown in Table 5. 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 use and 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

Table 3. 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

Table 4. Percentage Receipt and Median Time to Receipt of Post-progression Treatments in RCTs of Sipuleucel-T for the FDA-Approved Indication

Study	% placebo group receiving Frozen Salvage Product	Median time to receipt of Frozen Salvage Product(months)	Treatment group	% each group receiving docetaxel chemotherapy	Median time to receipt of docetaxel chemotherapy (months	% of each group receiving any other treatment besides Frozen Salvage Product	Median time to receipt of any other treatment besides Frozen Salvage Product (months)
IMPACT (17)	63.7	5.7	Sipuleucel-T	57.2	7.2*	81.8	NA
			Placebo	50.3	9.6*	73.1	
D9901 (24,25,28)	75.6	4.6**	Sipuleucel-T	35.9	NA	54.4	NA
			Placebo	47.6		62.8	
D9902A (24,25,28)	66.7	4.6**	Sipuleucel-T	38.6***	NA	66.7***	NA
			Placebo	34.4***		54.5***	

*Numbers differ from published article. Published article cites Kaplan-Meier estimate of median time to chemotherapy, which takes into account censoring due to death and/or end of follow-up.
**Number not available directly, number provided is from pooled analysis of D9901 and D9902
*** Number not available directly, estimated by subtracting numbers from D9901 from pooled (D9901 + D9902A)

Table 5. Alternative Analyses Taking into Account Incidence and Time of Docetaxel Treatment after Disease Progression

Sensitivity analysis	Study (ref)	Treatment effect hazard ratio (95% CI)	p value
Censor patients at time of docetaxel initiation	IMPACT (11)	0.649 (0.469, 0.898)	0.009
Time-dependent covariate for docetaxel use	IMPACT (11)	0.777 (0.615, 0.981)	0.034
"adjustment for time to docetaxel chemotherapy"*	D9901 (10)	0.649 (0.420, 1.000)	0.052
"adjustment for time to docetaxel chemotherapy"*	D9902A (10)	0.667 (0.398, 1.111)	0.121

*Methodology not specifically stated, most likely time-dependent covariate for docetaxel use

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.

Although these analyses show a statistically significant treatment hazard ratio of sipuleucel-T similar in magnitude to the primary analyses, it is not certain that they can fully account for the potential confounding effects of docetaxel treatment. They do 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 particular analytic issue in these studies is called" time-dependent confounding," and analytic techniques known as marginal structural models have been proposed as a method to overcome the potential biases that can occur under these circumstances.[38] (Personal communication, Bryan Shepherd, Ph.D., October 2010)

In sum, in three trials of similar design, 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 has 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. A synthesis of the evidence for the FDA-labeled indication using the modified AHRQ/GRADE framework is shown in Appendix Table A4. The body of evidence was graded as moderate. 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.

Key Question 1a.

For the FDA-labeled indication, 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?

Examination of treatment effects in separate subgroups may provide insight regarding possible treatment modifiers. If such effects are significant and biologically plausible, they may affect recommendations for treatment in specific types of patients. However, examination of subgroup effects is subject to statistical problems. Because of small sample sizes of particular subgroups, the statistical power to obtain statistically significant interactions is low. Because of the potentially large number of possible subgroup analyses, any particular finding may be due to chance. Because two of the three sipuleucel-T RCTs were fairly small in size, these problems are compounded. 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.

Treatment effects by baseline characteristics of patients are only presented in graphical form in any of the documents reviewed for this technology assessment (Appendix B). In Higano et al., subgroup effects by baseline patient characteristics were shown for a combined analysis of studies D9901 and D9902A (Appendix Figure B1).[24] The same baseline characteristics are examined for study D9901 alone in the Dendreon briefing document.[10] Many of the of the subgroup pairings show that the hazard ratio estimate is different depending on the subgroup comparison. For example, the most extreme difference depicted in the pooled analysis in Appendix Figure B1 is the analysis categorizing bone metastases. The group with 10 or fewer metastases shows a hazard ratio of greater than 2, indicating a strong effect of sipuleucel-T, whereas the group with more than 10 metastases shows a much weaker effect, probably close to 1.3 by visual estimation. If these point estimates were correct in terms of an actual interaction, it would mean that sipuleucel-T is very beneficial to patients with 10 or fewer metastases, and not very beneficial to patients with more than 10 metastases. However, 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.

A more extensive set of treatment effects by baseline characteristics was examined for the IMPACT trial (Appendix Figure B2). The broad confidence intervals surrounding most subgroup hazard ratios preclude raising significant concerns or suspicions regarding subgroup effects. The only exception to this is the analysis dividing the subjects of the IMPACT trial in age groups divided at 65 years of age. In the subgroup of subjects who were younger than 65 years, the hazard ratio was 1.411 (95 percent CI: 0.869–2.290), in the direction of harm of sipuleucel-T. The value of the hazard ratio for those 65 or older was not reported in any of the documents, but graphically its value was greater (closer to zero) than the overall hazard ratio for sipuleucel-T treatment effect, is it would have to be to counterbalance the 1.411 hazard ratio for the younger than 65 group. The confidence intervals of the two hazard ratios do not overlap,

indicating a highly statistically significant interaction if using statistical tests uncorrected for multiple statistical testing.

The FDA statistical review did a further pooled analysis of this possible age interaction using the pooled data from studies D9901, D9902A, and IMPACT. The results are shown below in Table 6.

Table 6. Subgroup analysis by age in pooled trials D9901, D9902A, and IMPACT

Group	Sipuleucel-T median survival (95% CI)	Placebo group median survival (95% CI)	Hazard ratio (95% CI)
Younger than 65 years	29.0 (22.8, 34.2)	28.2 (23.4, 32.5)	0.919 (0.618, 1.366)
65 years or older	23.4 (22.0, 27.1)	17.3 (13.5, 21.4)	0.661 (0.538, 0.813)

The pooled analysis shows a less extreme difference in the treatment effect in the two age groups, as the pooled hazard ratio for the younger than 65 age group is now in the direction of benefit of sipuleucel-T. However, estimate of benefit is less than the estimate for the subjects over age 65. It is inconclusive whether there is a treatment interaction with age at a cutoff of age 65.

In another analysis of pooled data, the FDA examined racial subgroups, and found consistent treatment benefit in Caucasian, African American, and other racial categories. However, the "other" racial category hazard ratio was not significant, mostly likely due to very small number of subjects in this category (a total sample size of 28).

In conclusion, limitations of sample size and multiple subgroup comparisons make it difficult to make inferences regarding the potential interaction of sipuleucel-T and baseline patient characteristics. A significant interaction with age group at an cutoff age of 65 was observed in the IMPACT results showing a qualitative interaction with hazard ratios indicating harm for those younger than 65 years and benefit for those 65 years or older. These subgroup differences became less extreme when all the clinical trial data was pooled, making the finding inconclusive.

Association of Cell Product Parameters, Patient Immune Response, and Patient Outcome

Although the dose of sipuleucel-T is not controlled or manipulated except to determine a minimum cell number in a dose, several measures of the product have been analyzed in relation to patient outcomes. It is uncertain what value these analyses have in the determination of the overall effectiveness of sipuleucel-T or if there is any clinical value to the associations found.

The analyses performed have all assessed product parameters and patient outcomes using only the sipuleucel-T-treated groups. The parameters that have been measured include the CD54 upregulation ratio, the total nucleated cell count, and the CD54 cell count, all analyzed as a cumulative total of these measures across the three doses given. Differentiating between a treatment effect versus a characteristic associated with inherent survival would require knowledge and analysis of these product parameters in the untreated control groups. Several of the types of measurements are not available or are probably not possible to do in untreated control groups. For example, in order to measure CD54 upregulation in placebo patients in the same way as in sipuleucel-T-treated subjects, the placebo patients' cells would need to be assayed for CD54 before and after culture in the presence of PA2024. However, as placebo patients, they would not receive the treated cells. It would be impossible to measure CD54 upregulation after the initial dose of drug, because CD54 upregulation tends to increase after the first exposure to sipuleucel-T. It is impossible to know what a placebo patient's CD54

upregulation would have been in subsequent doses of sipuleucel-T without treating them with an initial dose.

Table 7 shows a summary of the analyses of product parameters and patient survival reported from the three trials. In a pooled analysis of studies D9901 and D9902A, CD54 upregulation was correlated with survival and both unadjusted and analyses adjusted for baseline characteristics. Total nucleated cell count and CD54 count were not correlated with survival in final adjusted analyses. In the IMPACT study, the direction of the associations was similar to the prior pooled analysis, but the association between CD54 upregulation ratio and survival was not statistically significant, but the association between total nucleated cell count and survival was statistically significant. The results between the two studies show a consistent positive direction of associations, but apparently the strength of the association for a particular parameter varies between the studies. Confounding of the associations with unmeasured patient characteristics cannot be ruled out.

The table also shows some analyses reported from the IMPACT trial from a subset of subjects from that trial who had immune response assays performed. Two-hundred thirty-seven subjects had assay results available for antibody and T-cell proliferative responses to PA2024, PAP, and GM-CSF. These assays were done periodically up through week 26 of the study. Subjects with higher antibody responses to PA2024 and subjects with higher antibody responses to PAP had longer survival, but only the p value is reported. 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.

In sum, 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.

Table 7. Association of Sipuleucel-T Product Parameters and Patient Immune Response Measures and Patient Survival

Study (ref)	Product parameter/Patient immune response parameter	Measure of association	Value of association	p value
Pooled D9901 and D9902A (10) *Product parameters*	Cumulative CD54 upregulation ratio	Continuous, in Cox survival analysis	NR, positive correlation	0.009 unadjusted
			NR, positive correlation	0.022 adjusted
	Total nucleated cell count	Continuous, in Cox survival analysis	NR, positive correlation	0.018 unadjusted
			NR, positive correlation	0.138 adjusted
	CD54 cell count	Continuous, in Cox survival analysis	NR, positive correlation	0.354 unadjusted
			NR, positive correlation	0.694 adjusted
IMPACT (10) *Product parameters*	Cumulative CD54 upregulation ratio	Continuous, in Cox survival analysis	NR, positive correlation	0.123
	Total nucleated cell count	Continuous, in Cox survival analysis	NR, positive correlation	0.008
	CD54 cell count	Continuous, in Cox survival analysis	NR, positive correlation	0.016
IMPACT (11) *Immune response parameters*	Antibody titer against PA2024	>400 vs. ≤400, log-rank test	NR, >400 better survival	<0.001
	Antibody titer against PAP	>400 vs. ≤400, log-rank test	NR, >400 better survival	0.08
	T-cell proliferation assay PA2024	Unspecified, likely stimulation index >5 vs. ≤5, log-rank test	No association	NR
	T-cell proliferation assay PAP	Unspecified, likely stimulation index >5 vs. ≤5, log rank test	No association	NR

Consideration of Treatment Effect of Sipuleucel-T and Post-progression Chemotherapy

In a prior section of this technology assessment, it was considered whether post-progression chemotherapy was a potential confounder in determining the treatment effect of sipuleucel-T. It may also be of interest 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?

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.

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

Many of the studies of sipuleucel-T in which patients not meeting the FDA-labeled indications were enrolled 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.

We found seven sets of findings reported in five peer-reviewed publications and one conference abstract. One publication reports findings for two groups of patients. The description of the patients included in the studies, and therefore, the implied indications are:

- Metastatic castrate-resistant prostate cancer, but unspecified symptoms
- Nonmetastatic castrate-resistant prostate cancer
- Nonmetastatic hormone-sensitive prostate cancer

Brief summaries of the patient characteristics, treatment protocol, clinical and other outcomes are shown in Appendix Table A5. All the studies with the exception of the conference abstract are single-arm case series studies. The conference abstract is an RCT with relatively little description of the subjects and results available. Thus we did not do a formal quality rating of the studies, which is generally applicable to comparative treatment studies.

Metastatic Castrate-Resistant Prostate Cancer, but Unspecified Symptoms

Three case series comprising a total of 46 patients are reported.[12–14] The symptom status of the patients is not reported. However, the ECOG performance scores of the patients fall into the same range as those in the three previously reported clinical trials, so it is likely that these patient characteristics largely overlap with those in the RCTs for the labeled indication.

The clinical outcome reported in these case series was median time to progression. This varied between the studies from 12 to 19.3 weeks (Table 8). The protocols for assessing progression varied between the studies and were not always clearly explained in the studies. Given the lack of a control group, the studies do not provide information regarding the efficacy of sipuleucel-T in this patient group.

Other nonclinical outcomes included measurement of changes in PSA and assessments of T-cell proliferative responses to PA2024 and prostate antigens. T-cell proliferation increased from before treatment to after treatment. A few patients had PSA declines. However, the utility of PSA change as a marker of treatment response became questionable, as it was noted in both the study of Burch et al. (2000)[13] and Burch et al. (2004)[14] that a 50 percent decline in PSA in one patient in each study was accompanied by observable disease progression. One patient in Burch et al (2000)[13] had a fall in PSA to an undetectable level followed by regression and disappearance of metastatic disease.

Table 8. Results of Case Series of Sipuleucel-T in Metastatic Castrate-Resistant Prostate Cancer, Unspecified as to Symptoms

Study (ref)	Sample size	Median time to progression	Other results
Small et al., 2000 Phase I group (12)	12	12 weeks	T-cell proliferative response to PA2024 increases from 0 to 4 to 8 weeks No other results presented separately for phase I group
Burch et al., 2000 (13)	13	19.3 weeks	PSA 50% decline in 3 patients T-cell proliferative responses to PA2024, GM-CSF and PAP increase from time 0
Burch et al., 2004 (14)	21	16.9 weeks	PSA decline 25-50% in 2 patients PSA decline to undetectable in 1 patient long term T-cell proliferative responses to PA2024 increased from time 0 Increases in antibodies to PA2024 and GM-CSF

Nonmetastatic Castrate-Resistant Prostate Cancer

One case series study included patients with nonmetastatic castrate-resistant prostate cancer.[12] These patients are earlier in their stage of disease than those with metastatic disease. In general, these patients are identified with a rising PSA despite ADT, but they do not have metastases identified on imaging tests. Median time to progression in this set of patients was 29 weeks, which is indicative of their better prognosis than patients with metastases (Table 9). The case series design does not provide evidence as to the effectiveness of sipuleucel-T.

Table 9. Results of Case Series of Sipuleucel-T in Nonmetastatic Castrate-Resistant Prostate Cancer

Study (ref)	Sample size	Median time to progression	Other results
Small et al., 2000 Phase II group (12)	19	29 weeks	No other results presented separately for phase II group

Nonmetastatic Hormone-Sensitive Prostate Cancer

Two published case series studies and one RCT reported in a conference abstract have enrolled patients with nonmetastatic hormone-sensitive prostate cancer.[23,34,35] At this stage of disease, patients are generally asymptomatic, with the only sign of recurrent disease being a rising PSA level. Watchful waiting or ADT are recommended options at this stage of disease. The two case series studies were not intended to determine the efficacy of sipuleucel-T for this

indication, but to determine whether a particular rate of PSA decline greater than 50 percent could be achieved. In one study, bevacizumab (Avastin®, Genentech) was added to the treatment regimen. Both studies did not reach their intended primary outcome, with fewer than expected patients achieving a 50 percent or greater reduction in PSA. Patients were also followed for progression of disease, defined in both studies a doubling of pretreatment PSA or PSA 4 ng/mL or greater if pretreatment PSA was 2 or less, or development of distant disease. Patients leaving the study for other treatments or withdrawing consent were considered progression end points. The median time to progression was 11.7 months and 11.2 months in the two studies (Table 10). A proportion of patients in each study had some reductions in PSA values, and one study showed a statistically significant increase in post-treatment PSA doubling time compared to pretreatment PSA doubling time. Because there are no control groups, and the validity of PSA as an adequate outcome measure for this treatment is unknown, these case series do not provide evidence of efficacy of sipuleucel-T for this indication.

Table 10. Results of Case Series of Sipuleucel-T in Nonmetastatic Hormone-Sensitive Prostate Cancer

Study (ref)	Sample size	Median time to progression	Other results
Beinart et al., 2005 (34)	19	11.7 months (withdrawals for alternative treatment considered progression)	Negative result for primary outcome, zero patients with 50% reduction PSA 7/18 patients with 6-33% reduction of PSA No significant difference in pretreatment and post-treatment PSA doubling time
Rini et al., 2006 (35)	22	11.2 months	Negative result for primary outcome, 1/21 patients with 50% reduction PSA 9/21 patients with any decrease in PSA Significant increase post-treatment PSA doubling time compared to pretreatment

One RCT for this indication has some information available. Details of the design, inclusion and exclusion criteria of the PROTECT clinical trial are described in clinicaltrials.gov, and a brief summary of preliminary results are available in a conference abstract.[23,36] The PROTECT trial enrolled patients with recurrent prostate cancer as demonstrated by a rising PSA after initial prostatectomy. They were to be given 3 months of hormonal therapy, then randomized to sipuleucel-T or placebo infusion, using the regimen of treatment as in the previously reviewed RCTs. The principal outcome was biochemical failure defined as a PSA 3 ng/mL or greater. A booster dose would be given at the time of biochemical failure. End points to be assessed beyond the time of biochemical failure would include time to distant metastasis, PSA doubling time, and overall survival.

The clinical outcomes of this trial are shown in Table 11. The principal outcome of biochemical failure was not significant. Median time to biochemical failure was 18 months in the sipuleucel-T treated group and 15.4 months in the placebo group. Distant failure is also in favor of sipuleucel-T but not statistically significant. At the time of the analysis only 16 percent of patients had attained this end point. There was a statistically significant increase in PSA doubling time in the treated group compared to placebo group. Given the lack of detailed information about this study, and the non-significant principal clinical end point assessed so far, this study does not provide adequate evidence of efficacy of sipuleucel-T for this indication.

Table 11. Results of a Randomized Trial of Sipuleucel-T in Nonmetastatic Hormone-Sensitive Prostate Cancer

Study (ref)	Sample size	Principal outcome: Median time to biochemical failure	p value	Other results
PROTECT, Beer et al., 2007 (23, 36)	176	Treatment: 18.0 months Control: 15.4 months hazard ratio=0.94	>0.05	Time to distant metastasis HR 0.73 (p>0.05), point estimate in favor of sipuleucel-T PSA doubling time increased in sipuleucel-T group compared to placebo group (p=0.046)

Key Question 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?

Since none of the studies provide evidence of efficacy of sipuleucel-T for off-label indications, this question is moot.

Key Question 3.

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

For several reasons, the issue of the adverse effects of sipuleucel-T is complex. For one, the patients are in an age group where comorbidities are common. 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, 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.

The control groups of the randomized clinical trials did not receive a truly inert placebo. They 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.

In addition, 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.

Because the studies of sipuleucel-T that enrolled patients for off-label indications were early studies that used different dosages and treatment protocols than the randomized trials, and each of the three randomized trials for labeled indications is relatively small, this report uses a pooled analysis of all the randomized trials for the analysis of adverse events. This pooled safety analysis is reported in an FDA clinical review.[17] In addition to the three RCTs for the FDA-labeled indication (IMPACT, D9901, D9902A), the PROTECT trial for an off-label indication is included. The number of patients included in the pooled safety analysis is 601 patients treated with sipuleucel-T and 303 placebo-treated patients, of which 176 are from the PROTECT trial (allocated 2:1 sipuleucel-T:placebo). The pooled analysis provides the largest sample size and the best opportunity of detecting adverse events. The initial treatment protocol for administering sipuleucel-T was identical for all trials.

However, the FDA safety review in this document is a long detailed section over 40 pages in length with numerous tables, case reports, and unquantified descriptions of analysis. We will focus this presentation 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. Brief descriptions and summaries of other safety analyses are provided in Appendix Table A6.

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.

Deaths Occurring Proximate to Treatment

Four deaths occurred within 30 days after receiving infusions, 3 (0.5 percent) in the sipuleucel-T group and 1 (0.3 percent) in the placebo group. One subject in the sipuleucel-T group appears to have had a possible transient cerebrovascular event on the day of the third infusion, and had a fatal stroke 2 weeks after the third infusion. The other 3 deaths all appear to have been due to cancer progression.

Nonfatal Serious Adverse Events

A serious adverse event is defined as any adverse drug experience that results in any of the following outcomes; death, a life-threatening experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or the judgment of the investigator that medical or surgical intervention might be needed to prevent one of these outcomes.

Table 12 shows the incidence of serious adverse events classified according to preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA) classification system for coding adverse events. The overall incidence is similar between sipuleucel-T and placebo-

treated groups (24.0 percent versus 25.1 percent). Small numbers preclude the ability to make strong statistical conclusions regarding the risk of any single type of event. Events that occurred in more than 1 percent of subjects and more often in the treated group than the placebo group included pyrexia, spinal cord compression, chills, and dyspnea.

These adverse events were also recategorized by system organ class (data not shown). Adverse events that were at least 1 percent more frequent in the sipuleucel-T group than the placebo group included nervous system disorders, general disorders and administration site conditions, and musculoskeletal and connective tissue disorders. Most of the nervous system disorders were cerebrovascular events and transient ischemic attacks. These were analyzed in another analysis to be presented shortly. With the exception of pyrexia and chills, most of these adverse events occurred more than 14 days after the last treatment infusion. Thus the causality of the event to treatment is uncertain. Pyrexia and chills are symptoms consistent with an acute reaction to infusion, and will be analyzed again in another separate analysis.

In another similar analysis using the National Cancer Institute Common Toxicity Criteria for Adverse Events, adverse events were graded on a 1 to 5 scale, with 5 being the most serious adverse event of fatality. The incidence of grade 3 to 5 (serious to fatal) adverse events was similar between sipuleucel-T and placebo groups (30.9 percent and 32.0 percent, respectively).

Cerebrovascular Events

Due to a safety analysis done during a prior review of sipuleucel-T in 2007, specific attention was applied to the incidence of cerebrovascular events (CVE). As a condition of approval, FDA has required that the incidence of CVEs be assessed in a post-marketing surveillance study. Table 13 summarizes the incidences and types of CVEs from the 4 randomized trials. Overall, a higher incidence of CVEs occurred in the sipuleucel-T-treated group than the placebo group. The small number of specific types of events makes it difficult to make conclusions about these events. An exploration of the underlying risk factors for CVE showed several slight imbalances between groups in the risk factors for CVE, with the placebo group having lower prevalence of several risk factors for CVE, such as lower age, lower prevalence of hypertension, lower composite prevalence of several cardiovascular risk factors, and lower prevalence of prior cerebrovascular event. Thus although the incidence of CVE was higher in the sipuleucel-T group, the difference was small (absolute risk difference 1.1 percent) and it is possible that underlying risk factors could explain this difference. CVE-associated deaths were also compared. There were slightly more fatal CVEs in the sipuleucel-T group (1.4 percent versus 0.7 percent). The difference is too small to make definitive conclusions.

Table 12. Serious Nonfatal Adverse Events (SAE) Classified by Preferred Term and Treatment Group

Serious Adverse Event	Sipuleucel-T n=601 n (%)	Placebo n=303 n (%)
Any subject reporting SAE	144 (24.0)	76 (25.1)
Cerebrovascular Accident	11 (1.8)	6 (2.0)
Pyrexia	**10 (1.7)**	**1 (0.3)**
Spinal Cord Compression	**7 (1.2)**	**2 (0.7)**
Chills	6 (1.0)	0
Dehydration	6 (1.0)	4 (1.3)
Dyspnea	**6 (1.0)**	**1 (0.3)**
Atrial Fibrillation	5 (0.8)	4 (1.3)
Transient Ischemic Attack	**5 (0.8)**	**1 (0.3)**
Back Pain	4 (0.7)	6 (0.7)
Catheter Sepsis	4 (0.7)	4 (0.4)
Hematuria	4 (0.7)	8 (0.9)
Nausea	4 (0.7)	6 (0.7)
Prostate Cancer Metastatic	4 (0.7)	8 (0.9)
Pulmonary Embolism	4 (0.7)	6 (0.7)
Staphylococcal Bacteremia	**4 (0.7)**	**0**
Anemia	3 (0.5)	2 (0.7)
Arthralgia	3 (0.5)	0
Cardiac Failure Congestive	3 (0.5)	3 (1.0)
Osteoarthritis	**3 (0.5)**	**1 (0.3)**
Pneumonia	3 (0.5)	3 (1.0)
Sepsis	3 (0.5)	3 (1.0)
Staphylococcal Sepsis	**3 (0.5)**	**0**
Subdural hematoma	3 (0.5)	1 (0.3)
Syncope	3 (0.5)	1 (0.3)
Acute Myocardial Infarction	**2 (0.3)**	**0**
Asthenia	2 (0.3)	1 (0.3)
Atrial Flutter	**2 (0.3)**	**0**
Bacteremia	2 (0.3)	1 (0.3)
Brain Mass	**2 (0.3)**	**0**
Catheter Bacteremia	**2 (0.3)**	**0**
Cerebral Infarction	**2 (0.3)**	**0**
Cervical Vertebral fracture	**2 (0.3)**	**0**
Chest Pain	**2 (0.3)**	**0**
Chest Wall Pain	**2 (0.3)**	**0**
Chromic Myelomonocytic Leukemia	**2 (0.3)**	**0**
Coronary Artery Disease	2 (0.3)	2 (0.7)
Disseminated Intravascular Coagulation	2 (0.3)	1 (0.3)

Table 12. Serious Nonfatal Adverse Events (SAE) Classified by Preferred Term and Treatment Group (continued)

Serious Adverse Event	Sipuleucel-T n=601 n (%)	Placebo n=303 n (%)
Gait Disturbance	**2 (0.3)**	**0**
Gastrointestinal Hemorrhage	**2 (0.3)**	**0**
Hemorrhage Intracranial	**2 (0.3)**	**0**
Hyperhidrosis	**2 (0.3)**	**0**
Hypertension	**2 (0.3)**	**0**
Hypoxia	**2 (0.3)**	**0**
Infusion-Related Reaction	**2 (0.3)**	**0**
Intervertebral Disc Protrusion	**2 (0.3)**	**0**
Intestinal Obstruction	2 (0.3)	1 (0.3)
Lacunar Infarction	**2 (0.3)**	**0**
Metastasis to Spine	**2 (0.3)**	**0**
Muscular weakness	2 (0.3)	1 (0.3)
Myocardial Infarction	2 (0.3)	1 (0.3)
Myocardial Ischemia	2 (0.3)	1 (0.3)
Pain in Extremity	**2 (0.3)**	**0**
Pathological Fracture	2 (0.3)	1 (0.3)
Pleural Effusion	2 (0.3)	1 (0.3)
Tachycardia	**2 (0.3)**	**0**
Urinary Tract Retention	2 (0.3)	4 (1.3)
Urinary Tract Retention	2 (0.3)	1 (0.3)

Bold print indicates a higher incidence in sipuleucel-T treated group than in placebo-treated group

Table 13. Summary of Incidence and Characteristics of Cerebrovascular Events

	Sipuleucel-T n=601 n (%)	Placebo n=303 n (%)
Cerebrovascular event incidence (including TIA)	24 (4.0 %)	9 (2.9 %)
Ischemic stroke	16 (2.7%)	8 (2.6%)
Hemorrhagic stroke	4 (0.7%)	1 (0.3%)
Unknown stroke	4 (0.7%)	0
Transient ischemic attack (TIA)	5 (0.8%)	1 (0.3%)

Infections

Due to the manufacturing and infusion process of sipuleucel-T, there is the possibility of infections due to the product or the venous catheters need to infuse the treatment. The placebo group, because it also underwent leukapheresis and infusion, does not represent a "background" rate of infection of a true untreated control group. Infections specifically identified as catheter-related infections should be viewed as the risk of infection related to treatment regardless of treatment group. Infections occurring proximate in time to leukapheresis and infusion might be related to treatment, but attribution is difficult.

Overall, similar percentages of subjects developed infection adverse events, 27.5 percent in the sipuleucel-T group and 27.7 percent in the placebo group (Table 14). These overall incidences of infection in either group may not be related to sipuleucel-T or placebo treatment. However, 15.3 percent and 14.5 percent of subjects in each group developed infections within one week of their final infusion. Some of these infections in either group may possibly be related to leukapheresis and/or infusion. Infections designated as catheter-related occurred overall in 3 percent of subjects (sipuleucel-T group 3.2 percent, placebo group 2.6 percent) and would not have occurred but for treatment-related procedures. Infections occurring late in the clinical trials (after 16 weeks or disease progression) are not reported unless attributed to sipuleucel-T, according to the protocol for reporting adverse events.

Table 14. Summary of Various Incidence Rates of Infections

Infection outcome	Sipuleucel-T n=601 n (%)	Placebo n=303 n (%)
Infection adverse event during study	165 (27.5%)	84 (27.7%)
Infection events within one week of final infusion	NR (15.3%)	NR (14.5%)
Infection event grade 3 or higher severity	30 (5%)	10 (3.3%)
Catheter-related infection	19 (3.2%)	8 (2.6%)

Finally, it is noted in this section of the FDA review that sterility tests are done on the infusion product but results are not available until some days after infusion. Three patients in the IMPACT study received products that were found to be contaminated; two of three developed infection adverse events, one which was grade 4 severity. Thus it appears that sipuleucel-T treatment is associated with increased risk of infections, and that there is a possibility of product contamination leading to infection.

Infusion Reaction Adverse Events

Exploration of incidence of commonly reported adverse events of usually low severity led to an analysis of incidence of adverse events which are commonly associated with infusion reactions. An analysis was performed using terms that are included in the National Cancer Institute Common Terminology Criteria for Adverse Events for infusion reaction syndrome.

Table 15 shows the incidence of overall infusion reaction-related adverse events and each separate term, for adverse events occurring within 1 day of infusion. Overall, the incidence of any infusion reaction adverse event was much higher in the sipuleucel-T treated group than the placebo group, 71.4 percent versus 28.7 percent. In terms of severe infusion reactions rated grade 3 severity, these occurred in 21 subjects in the sipuleucel-T group and none in the placebo group. Seven subjects in the sipuleucel-T group were hospitalized for management of an acute infusion reaction.

Adverse Event Interactions

There is a brief text description in the FDA review describing analyses regarding associations of adverse events with product parameters and patient characteristics. Very little quantitative data is presented in this section, so results will simply be paraphrased from the FDA review. There seemed to be no association between adverse events and the product parameters of total nucleated cell count, CD54 cell count, and CD54 upregulation. There was slightly higher incidence of adverse events associated with infusion reactions in subjects younger than 65 years old. None of the differences appeared to be clinically important. There were not enough African American subjects in the study for meaningful analysis of possible racial interactions.

Summary of Adverse Effects Review

Despite the presence of confounding issues relating to the study design of the randomized clinical trials, there are a few solid conclusions that can be reached. Sipuleucel-T infusions can cause symptoms consistent with an infusion reaction, usually within 1 day of infusion, of greater frequency than a placebo infusion. Thus the causality of the activated product causing such reactions is quite certain. These infusion reactions were occasionally severe; 21 out of 601 patients had grade 3 severity infusion reactions, and 7 required hospitalization.

Sipuleucel-T is also associated with infections, 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.

For all other serious types of 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.

Table 15. Incidence of Infusion Reaction Adverse Events Within 1 Day of Infusion

Adverse Event by Preferred Term	Sipuleucel-T n=601 n (%)	Placebo n=303 n (%)
Any adverse event	428 (71.4)	87 (28.7)
Chills	300 (49.9)	16 (5.3)
Pyrexia	146 (24.3)	6 (2.0)
Fatigue	126 (21.0)	43 (14.2)
Headache	72 (12.0)	6 (2.0)
Nausea	71 (11.8)	7 (2.3)
Myalgia	47 (7.8)	7 (2.3)
Arthralgia	33 (5.5)	10 (3.3)
Hypertension	29 (4.8)	2 (0.7)
Asthenia	28 (4.7)	10 (3.3)
Dizziness	25 (4.2)	6 (2.0)
Hyperhidrosis	21 (3.5)	0
Malaise	17 (2.8)	4 (1.3)
Dyspnea	16 (2.7)	1 (0.3)
Flushing	13 (2.2)	7 (2.3)
Hypotension	11 (1.8)	1 (0.3)
Rash	8 (1.3)	2 (0.7)
Hot Flush	7 (1.2)	4 (1.3)
Lethargy	7 (1.2)	0
Cough	6 (1.0)	3 (1.0)
Hypoxia	5 (0.8)	0
Urticaria	4 (0.7)	0
Feeling Hot	3 (0.5)	0
Tachycardia	3 (0.5)	0
Bronchospasm	2 (0.3)	0
Pruritus	2 (0.3)	2 (0.7)
Any grade 3 infusion reaction	21 (3.5)	0
Hospitalization for infusion reaction serious adverse events	7 (1.2)	0

Conclusions/Future Research Issues

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.

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Appendix A. Appendix Tables

Appendix Table A1. Inclusion/Exclusion Criteria and Baseline Characteristics of RCTs of Sipuleucel-T in Castrate-Resistant Prostate Cancer

Study (ref)	Inclusion/exclusion criteria	Baseline characteristic	Sipuleucel-T	Placebo	Comment
IMPACT (11)	Inclusion: metastatic CRPC, asymptomatic or minimally symptomatic, PSA >5, testosterone<50, progressive disease by PSA or imaging, expected survival of ≥6 months Exclusion: ECOG performance ≥2, visceral metastases, pathologic fractures, spinal cord compression, recent treatment (28 days) with steroids, radiation, surgery, systemic therapy, or change in bisphosphonate therapy, past history of >2 chemotherapy regimens, chemotherapy within the past 3 months	Median age	72	70	Original protocol required asymptomatic CRPC, Gleason score≤7
		% white	89.4	91.2	
		%Gleason score ≤7	75.4	75.4	
		% ECOG score 0	82.1	81.3	
		Metastasis bone only	50.7	43.3	
		Metastasis soft tissue	7.0	8.2	
		Metastasis both	41.9	48.5	
		Median PSA	51.7	47.2	
		Median PAP	2.7	3.2	
		Median LDH	194	193	
		Median alk phos	99	109	
		% prior chemotherapy	19.6	15.2	
D9901 (29)	Mostly similar to IMPACT, some differences Different inclusion: only asymptomatic CRPC, 25% staining of tumor for PAP Different exclusion: slight differences in prior therapies allowed and time since prior therapies	Median age	73	71	
		% white	89	93.3	
		%Gleason score ≤7	61	55.6	
		% ECOG score 0	75.6	82.2	
		Metastasis bone only	42.7	26.7	
		Metastasis soft tissue	6.1	8.9	
		Metastasis both	51.2	64.4	
		Median PSA	46	47.9	
		Median PAP	7	6.5	
		Median LDH	173.5	172	
		Median alk phos	102	92	
		% prior chemotherapy	3.7	8.9	

Appendix Table A1. Inclusion/Exclusion Criteria and Baseline Characteristics of RCTs of Sipuleucel-T in Castrate-Resistant Prostate Cancer (continued)

Study (ref)	Inclusion/exclusion criteria	Baseline characteristic	Sipuleucel-T	Placebo	Comment
D9902A (10)	Identical to D9901	Median age	70	71	
		% white	90.8	93.9	
		% Gleason score ≤7	68.7	51.5	
		% ECOG score 0	78.5	69.7	
		Metastasis bone only	47.7	30.3	
		Metastasis soft tissue	10.8	21.2	
		Metastasis both	41.5	48.5	
		Median PSA	61.3	44.0	
		Median PAP	4.5	5.1	
		Median LDH	187	179	
		Median alk phos	140	105	
		% prior chemotherapy	11.1	9.1	

Abbreviations: alk phos: alkaline phosphatase; CRPC: castrate-resistant prostate cancer; ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; PAP: prostatic acid phosphatase; PSA: prostate-specific antigen;

Appendix Table A2. Quality Assessment of RCTs of Sipuleucel-T

Study	Initial Assembly of Comparable Groups	Low Loss to Followup, Maintenance of Comparable Groups	Measurements Reliable, Valid, Equal	Interventions Comparable, Clearly Defined	Appropriate Analysis of Results	Funding or Sponsorship Source Acknowledged	Overall Rating
IMPACT	Y Randomization method specified, stratified by Gleason, bone metastases, bisphosphonate use	U Low loss to follow-up Design caused delay in chemotherapy in control groups	Y Disease progression blinded end point Objective survival end point	U Treatment clearly defined, potential confounding effects of placebo leukapheresis, frozen sipuleucel-T salvage treatment, unblinding after progression, and unbalanced post-progression treatment	Y Prespecified survival analysis Sensitivity analysis for confounding effects	Y	FAIR
D9901	Y Randomization method specified, stratified by center, bisphosphonate use	U Low loss to follow-up Design caused delay in chemotherapy in control groups	Y Disease progression blinded end point Objective survival end point	U Treatment clearly defined, potential confounding effects of placebo leukapheresis, frozen sipuleucel-T salvage treatment, unblinding after progression, and unbalanced post-progression treatment	U Survival analysis not prespecified Disease progression end point specified	Y	FAIR
D9902A	Y Randomization method specified, stratified by center , bisphosphonate use	U Low loss to follow-up Design caused delay in chemotherapy in control groups	Y Disease progression blinded end point Objective survival end point	U Treatment clearly defined, potential confounding effects of placebo leukapheresis, frozen sipuleucel-T salvage treatment, unblinding after progression, and unbalanced post-progression treatment	U Survival analysis not prespecified Disease progression end point specified	Y	FAIR

Abbreviations: U: unclear; Y: Yes

Appendix Table A3. Description of Issues Regarding Alternative Analyses of Survival Outcomes in the RCTs of Sipuleucel-T

Type of analysis (ref)	Study	Discussion
Single variable adjusted estimate of sipuleucel-T treatment effect (32, 33)	D9901	Most analyses adjusting for a single baseline characteristic find a statistically significant hazard ratio for sipuleucel-T treatment effect in FDA statistical review.
	IMPACT	Various analyses adjusting for each of 21 baseline factors described as consistent with sipuleucel-T treatment effect in FDA statistical review.
Multivariable adjusted estimate of sipuleucel-T treatment effect (32, 33)	D9901	Hazard ratio adjusted for 5 variables showed treatment hazard ratio of 0.47, p<0.002. FDA statistical review showed this analysis has missing values which result in exclusion of short surviving sipuleucel-T patients and long surviving placebo patients. FDA statistical review shows other models with hazard ratio not significant.
	D9902A	Hazard ratio adjusted for 5 variables showed treatment hazard ratio of 0.52, p=0.023. FDA statistical review showed this analysis has missing values which result in exclusion of short surviving sipuleucel-T patients and long surviving placebo patients.
	IMPACT	Overall survival adjusting for additional baseline prognostic factors described as consistent with primary analysis in FDA statistical review.
Prostate cancer-specific survival (10, 11)	IMPACT	Hazard ratio for treatment effect of 0.77, p=0.02. Most deaths in the study attributed to prostate cancer. Most cause-of-death algorithms likely to attribute death to prostate cancer.
	D9901	Hazard ratio for treatment effect of 0.49, p<0.002. Most deaths in study (77/94) attributed to prostate cancer. Most cause-of-death algorithms likely to attribute death to prostate cancer.
	D9902A	Hazard ratio for treatment effect of 0.74, p=0.287. Most cause-of-death algorithms likely to attribute death to prostate cancer.

Appendix Table A4. Overall Grade of Strength of Comparative Study Evidence for FDA-labeled Indication for Sipuleucel-T

Study Design	Risk of bias	Consistency	Directness	Precision	Overall Grade/Conclusion
3 randomized clinical trials. The design provides the strongest evidence for treatment efficacy	The trial design resulted may have resulted in a systematic difference in the subsequent initiation of chemotherapy. Chemotherapy was less frequent and later in the control groups due to use of frozen salvage product. Statistical adjustment methods used do not account for time-dependent confounding. It cannot be assumed that frozen salvage product produces a conservative bias, because it is not the same as sipuleucel-T	The survival findings of the studies are consistent in direction and magnitude. Disease progression outcomes showed no difference.	The outcome of overall survival is the most direct and least subject to bias.	According to a narrow definition of precision based strictly on the magnitude and confidence interval of the treatment effect, along with the consistent direction of 3 studies, the results are precise.	The strength of the body of evidence for this indication is moderate. Concerns regarding bias are the principal reason for this conclusion.

Appendix Table A5. Description of Characteristics of Studies for Off-Label Indications for Sipuleucel-T

Author/Indication (ref)	Patients included	Treatment Protocol	Clinical Outcomes	Other Outcomes
Small et al., 2000 Phase I group (12) Unspecified metastatic CRPC	Median age 67.5 Median PSA 209 ECOG range 0-1	Escalating dose at 0, 4, 8 weeks, and 24 weeks to stable or improving pts	Time to disease progression	T-cell responses PAP antibodies 50% decrease in serum PSA
Burch et al., 2000 (13) Unspecified metastatic CRPC	Median age 67.5 Median PSA 323 ECOG range 0-1	Standard dose at 0, 4 weeks. Injection of PA2024 at 8, 12, 16 weeks (3 dose levels of PA2024)	Time to disease progression	T-cell proliferation PAP antibodies GM-CSF antibodies
Burch et al., 2004 (14) Unspecified metastatic CRPC	Median age 72 Median PSA 221 % Gleason $\leq$7: 58	Standard dose at 0, 2 weeks. Injection of PA2024 at 4, 8, 12 weeks	Time to disease progression	Decrease in PSA Cellular response to PA2024
Small et al., 2000 Phase II group (12) Nonmetastatic CRPC	Median age 72 Median PSA 14.5 ECOG range 0-1	Standard dose at 0, 4, 8 weeks, and 24 weeks to stable or improving pts	Time to disease progression	T-cell responses PAP antibodies 50% decrease in serum PSA
Beinart et al., 2005 (34) Nonmetastatic hormone-sensitive recurrent PC	Median age 67 Median PSA 1.6 % Gleason $\leq$7: 84	Standard dose at 0, 2, 4 weeks		50% decrease in serum PSA Time to PSA progression PSA doubling time
Rini et al., 2006 (35) Nonmetastatic hormone-sensitive recurrent PC	Median age 70 Median PSA 2.3 % Gleason $\leq$7: 82	Standard dose at 0, 2, 4 weeks. Bevacizumab every 2 weeks until toxicity or progression		50% decrease in serum PSA Time to PSA progression PSA doubling time
PROTECT trial unpublished (23, 36) Nonmetastatic hormone sensitive recurrent PC	Primary therapy was radical prostatectomy No other data available	3 months of hormonal therapy, then randomized to standard dose or placebo infusion at 0, 2, 4 weeks. Booster dose of drug or placebo at biochemical failure.	Biochemical failure PSA $\geq$3 Time to distant failure Overall survival	PSA doubling time

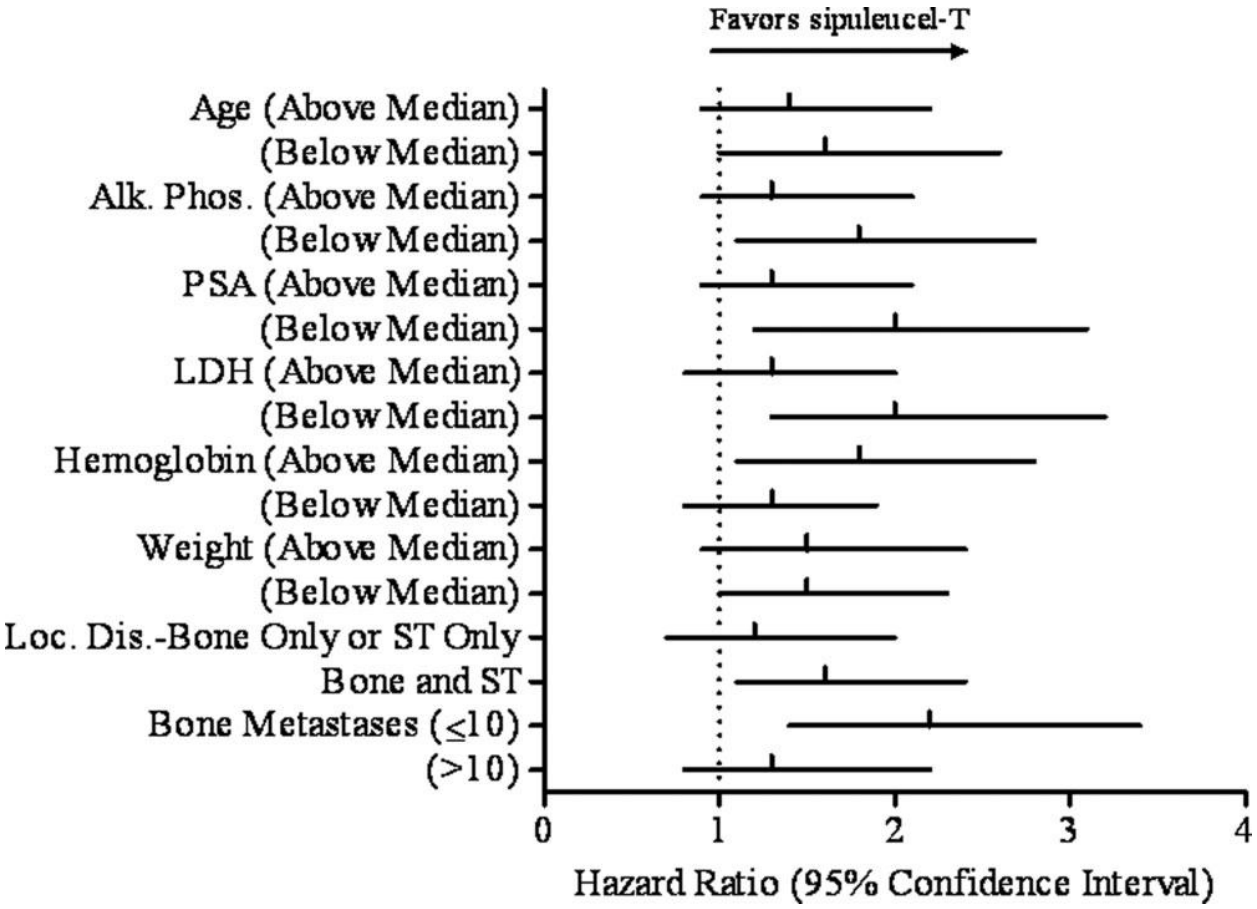
Abbreviations: CRPC: castrate-resistant prostate cancer; ECOG: Eastern Cooperative Oncology Group; GM-CSF: granulocyte-macrophage colony-stimulating factor; PAP: prostatic acid phosphatase; PC: prostate cancer; PSA: prostate-specific antigen;

Appendix Table A6. Summary of Other Types of Analysis of Adverse Events in FDA Clinical Review

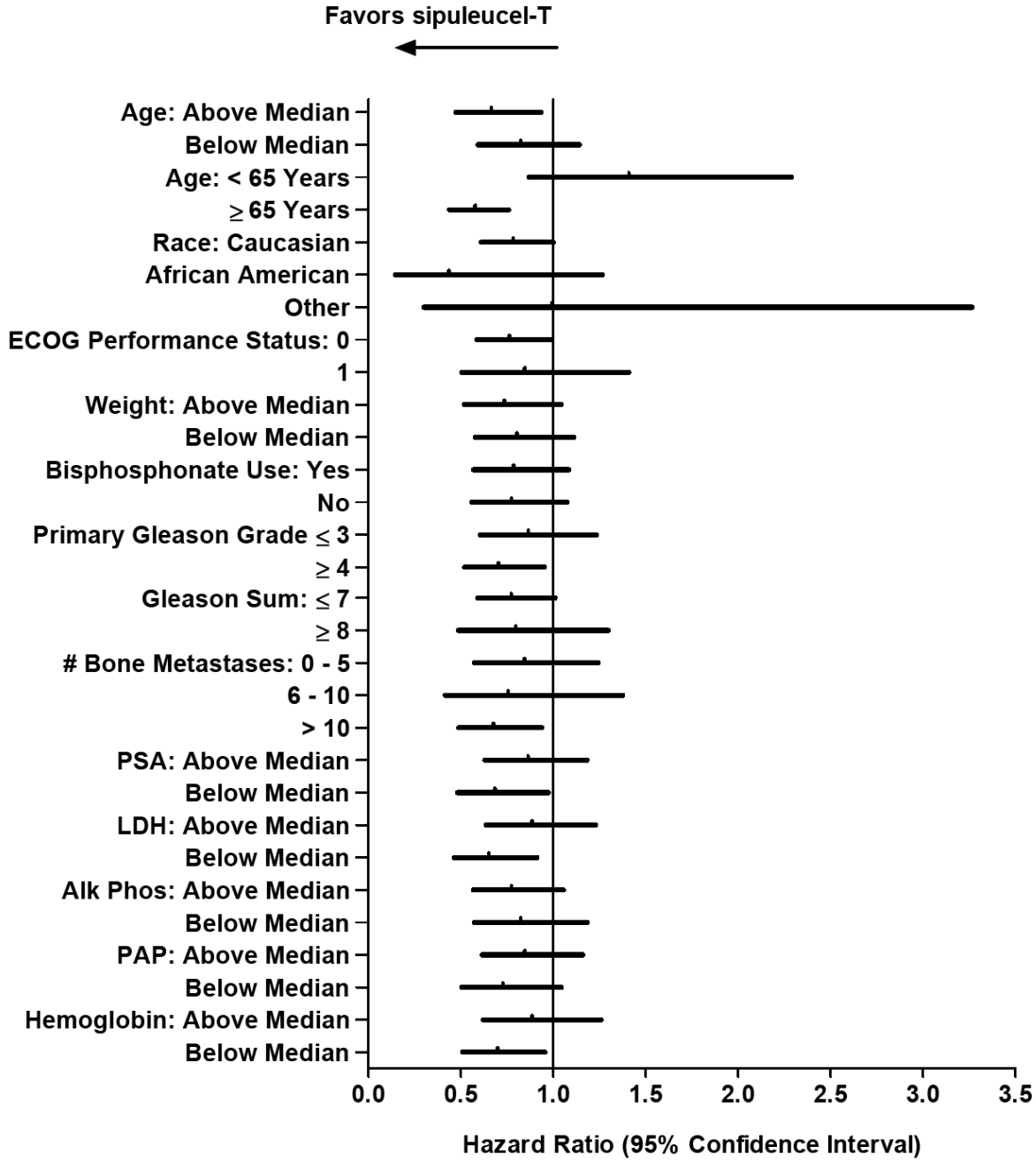
Description of type of adverse event or analysis	Summary of results and comment
Cause of death	No substantial difference in cause of death between sipuleucel-T-treated groups and placebo
Dropouts and/or Discontinuations	Very few patients dropped out due to treatment-related adverse events
Non-neurologic vascular events	No increased rate of arterial or venous vascular events in sipuleucel-T treated groups
New Primary Cancers	No difference between groups
Respiratory Reactions	Higher rate within one day in sipuleucel-T treated groups consistent with infusion reaction
Autoimmune disorders	No difference in rates of adverse events using subset of terms consistent with autoimmune disorders
Skin disorders	Higher rate of minor disorders in sipuleucel-T treated groups consistent with infusion reaction
Renal insufficiency	No notable differences between groups

APPENDIX B. Appendix Figures

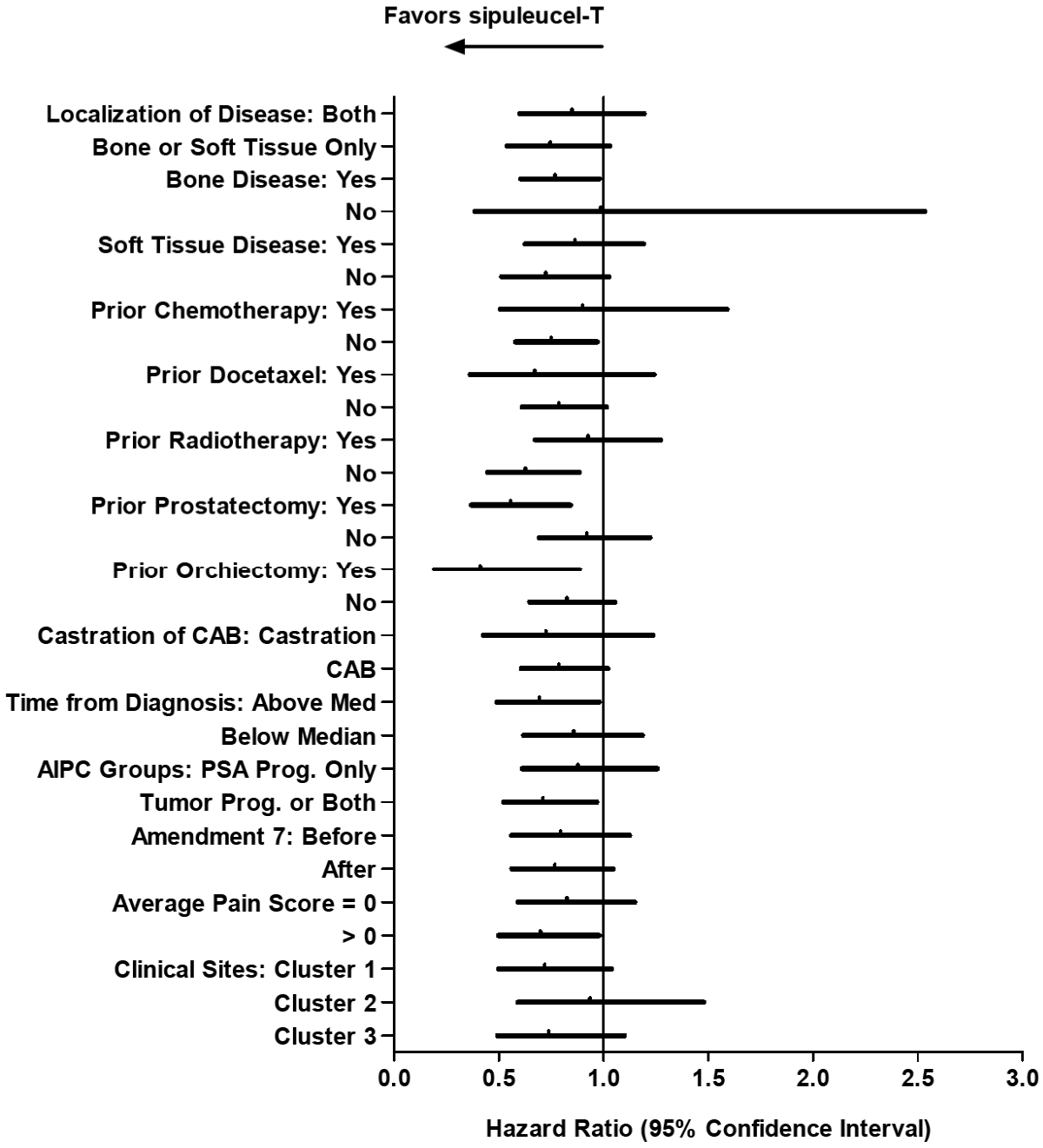
Appendix Figure B1. Sipuleucel-T treatment hazard ratios according to subgroups from the pooled D9901 and D9902 studies (reproduced from Higano et al. 2009[24]; permission pending)



Appendix Figure B2. Sipuleucel-T treatment hazard ratios according to subgroups from the IMPACT trial (reproduced from FDA Clinical Review[17])



Appendix Figure B2. Sipuleucel-T treatment hazard ratios according to subgroups from the IMPACT trial (reproduced from FDA Clinical Review[17], continued)



APPENDIX C. Search Strategy

The following electronic databases were searched for citations.

- MEDLINE® (inception [1948] through July 13, 2010)
- EMBASE® (inception [1974] through July 13, 2010)
- Cochrane Controlled Trials Register (no date restriction)

The MEDLINE® search resulted in 190 unique citations many of which were news-type articles so the search was limited to the following document types: Clinical Trial, Meta-Analysis, Practice Guideline, Randomized Controlled Trial, Comparative Study, Controlled Clinical Trial, Multicenter Study and that resulted in 23 records. The EMBASE® search resulted in 361 citations and was limited to restrict to articles, which resulted in 86 records. The Cochrane search resulted in 3 new citations.

In addition to the electronic database searches, we also examined the documents available on the U.S. Food and Drug Administration's website regarding the Dendreon submissions to the FDA for approval of this product. The bibliographies of all retrieved articles were also reviewed for citations to any RCT that was missed in the database searches. We did not systematically seek studies published in conference proceedings and abstracts.

MEDLINE search 7/13/10

1. provenge OR sipuleucel* OR Dendreon OR "APC-8015" = 87
2. (prostate OR prostatic) AND "dendritic cell*" = 115
3. 1 OR 2 = 190
4. 3 and Limits: Humans, Clinical Trial, Meta-Analysis, Practice Guideline, Randomized Controlled Trial, Comparative Study, Controlled Clinical Trial, Multicenter Study, English = 23
5. plus selective searching through the 187 from set 3 that weren't in set 4.

EMBASE search 7/13/10

1. 'provenge'/exp OR sipuleucel* OR dendreon OR 'apc 8015'/exp AND [humans]/lim AND [embase]/lim (not MEDLINE) = 321
2. 'prostate'/exp OR prostatic AND ('dendritic cell'/exp OR 'dendritic cells'/exp) AND [humans]/lim AND [embase]/lim = 55
3. 1 OR 2 = 361
4. 3 AND 'article'/it = 86