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Integration of immunotherapy into the management of advanced prostate cancer

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Abstract

Until recently, the only therapy shown to improve survival in men with metastatic castration-resistant prostate cancer (mCRPC) had been chemotherapy, usually reserved for symptomatic patients. However, sipuleucel-T, a cellular product directed toward a specific antigen, prostatic acid phosphatase, was Food and Drug Administration (FDA) approved in 2010 in the United States, based on phase 3 data showing improved overall survival in men with minimal or no symptoms due to mCRPC compared with placebo. Subsequently, several other promising immunotherapeutic approaches have advanced to study in the phase 3 setting, including ipilimumab and PROSTVAC. The demonstration of efficacy of immunotherapy in prostate cancer provides a new treatment option for men with no or few symptoms early in the course of mCRPC. Since sipuleucel-T was approved, several drugs that favorably impact survival have also been approved or are close to approval in the United States. These agents include cabazitaxel, abiraterone, radium-223, and MDV3100. There are many unresolved issues about sipuleucel-T, such as best timing in the course of mCRPC, the role for booster therapy, and the role of combinations with other active drugs, including other immune-modulating approaches. There are also many questions regarding sequencing of these new agents and, given the number of other promising agents in phase 3 trials, these questions will become more complicated, underscoring the need for better predictors of benefit for the individual patient.

Keywords: Immunotherapy; Prostrate cancer; Castrate resistant prostate cancer; Sipuleucel T

Introduction

The initial response to castration therapy in men with metastatic prostate cancer (CaP) is typically quite good, with most patients achieving a decline in prostate-specific antigen (PSA) and symptomatic improvement when pain was present at diagnosis. However, hormone sensitivity with control of PSA lasts only a few years in men with metastases before the disease progresses to castration-resistant prostate cancer (CRPC). In men with recurrent but nonmetastatic CaP, remissions generally last longer. Men with nonmetastatic CRPC will also ultimately develop metastases (mCRPC), and that length of time, which can be estimated from the initial level of PSA and the PSA doubling time, is often only about 2–3 years [1]. Before recent changes in the treatment landscape, the only treatment shown to prolong survival in mCRPC was docetaxel, which was approved by the FDA in 2004 [2–4]. Unfortunately, almost all patients who develop mCRPC will die from the disease.

A brief summary of the current landscape in CRPC treatment is displayed in Fig. 1. Many men with early stage mCRPC who have no symptoms do not want the toxicity of chemotherapy to worsen their quality of life and seek other options, which are now becoming available. These include sipuleucel-T, as well as the addition of denosumab for the prevention of skeletal-related events. For patients with post-docetaxel mCRPC, 2 new drugs have been approved by the FDA: abiraterone, an androgen synthesis inhibitor (Cyp 17

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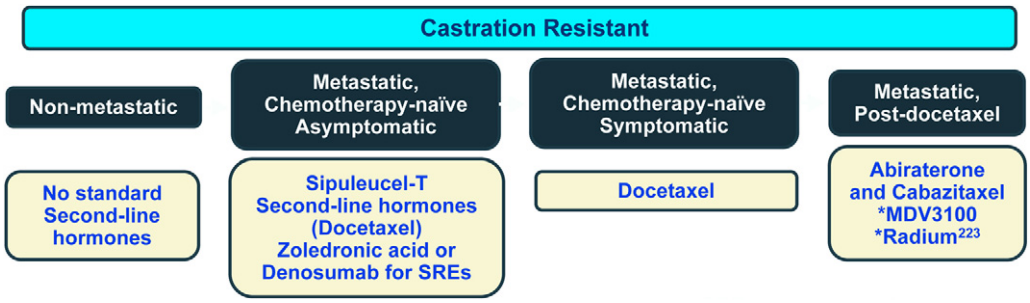

Fig. 1. Prostate cancer landscape.

lyase inhibitor) and cabazitaxel, a chemotherapy agent. Two others with positive phase 3 clinical trial results are MDV3100, an anti-androgen; and radium-223, an α-emitting radiopharmaceutical. The treatment of CaP is an increasingly complex landscape.

The emergence of immunotherapy in prostate cancer

Immunotherapy, that is, the treatment of existing cancer by inducing or enhancing an immune response, has now been shown to benefit patients with CaP. The history of this approach encompasses many years of work, numerous anecdotal reports of success, and promising theories that are not always accompanied by proof of concept or success in clinical trials.

Any list of the seminal discoveries in the field of immunotherapy that led to current CaP treatment must include the work of Steinman and Cohn, who discovered the dendritic cell in 1973 [5]. Subsequent work by Banchereau, who worked with Steinman, and others, first demonstrated the activity of antigen-presenting cells (APCs) and then explored APCs as mediators of immunotherapy, another very important advance [6]. Additional research by Dranoff et al. and others focused on granulocyte-macrophage colony-stimulating factor (GM-CSF), thought to be a hematologic growth factor, which was inserted into tumor cells using a retroviral vector [7]. The tumor cells were radiated and injected into animals as a vaccination. This work led to the understanding that GM-CSF is a potent stimulator of the immune system; it was later studied in clinical trials in humans. Krummel and Allison documented that cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) acts as a type of brake in the immune system to prevent the development of autoimmunity [8]. The development and introduction of an anti-CTLA-4 antibody was shown to stimulate the immune system and provide an antitumor effect [9].

Immune cells involved in the adaptive immune response

The interaction between the APC and the T cell is critical to the immune response. The APC stimulates T cells with processed antigens. CD4+ T cells recognize antigens and produce cytokines that activate T cell and/or B cell response, while sensitized CD8+ T cells attack and lyse cells that present with the target antigen [10]. Dendritic cells are required for T cell activation, which in turn is necessary for an effective antitumor response. Processing of proteins into peptides and presentation of those peptides on the surface of the APC so that they can be recognized by the T cell are critical parts of this process [10], as is the interaction between the co-stimulatory molecule B7 and CTLA-4 [11]. The helper T cells will secrete a variety of cytokines, which will stimulate cytotoxic T lymphocytes. These, in turn, are presumed to provide the antitumor effect and this cytotoxic T cell activity forms the basis of what is now termed dendritic cell therapy.

Several different approaches have been taken in the search for effective immunotherapy for CRPC [12]. Viral vectors, especially poxvirus-based vectors, have been employed to induce strong antibody responses. Antigen-specific immunotherapeutic approaches have focused primarily on PSA as a potential target. Other research has employed a more personalized, active immunization approach using agents individually manufactured for each patient. A cell-based immunotherapy approach has also been employed to provide a polyvalent approach to tumor immunotherapy. In addition, monoclonal antibodies have been developed as a passive form of immunotherapy. Four of the immunologic approaches with particular relevance to mCRPC are discussed in more detail below.

Sipuleucel-T

Sipuleucel-T is an autologous active cellular immunotherapy product that stimulates a T cell immune response against prostatic acid phosphatase (PAP). It is the first immunotherapy documented to prolong survival in mCRPC in a phase 3 trial (Fig. 2) [13]. A fusion antigen is first created by combining the prostate antigen PAP with GM-CSF. The mononuclear layer containing APCs is removed from the patient during leukapheresis (Fig. 3). The leukapheresis product is then shipped to a manufacturing facility where it is co-cultured with the fusion protein. After about 40 hours, the fusion protein is washed out of the product and the cellular product is then shipped back to the site and infused back into the patient. Presumably, activated T cells develop, directed at the PAP antigen on prostate

Fig. 2. Mechanism of action of sipleucel-T.

cancer cells. This procedure is completed approximately every 2 weeks for a total of 3 infusions (weeks 0, 2, 4).

The initial randomized sipuleucel-T trial (D9901) was led by Small [14]. A total of 127 men with asymptomatic mCRPC were randomly assigned to receive placebo (n = 45) or sipuleucel-T (n = 82) in a 1:2 fashion. The primary endpoint in this study was time to objective disease progression (TTP); the secondary endpoint was overall survival (OS). Crossover was allowed if the patient received placebo initially. At disease progression, these patients could receive a frozen version of the cells that had been exposed to the antigen. Approximately 50% of the patients who received the placebo opted to receive the vaccine.

TTP results were not statistically significant between the treatment arms. However, OS did differ despite the crossover design. The results were brought to the FDA for approval in

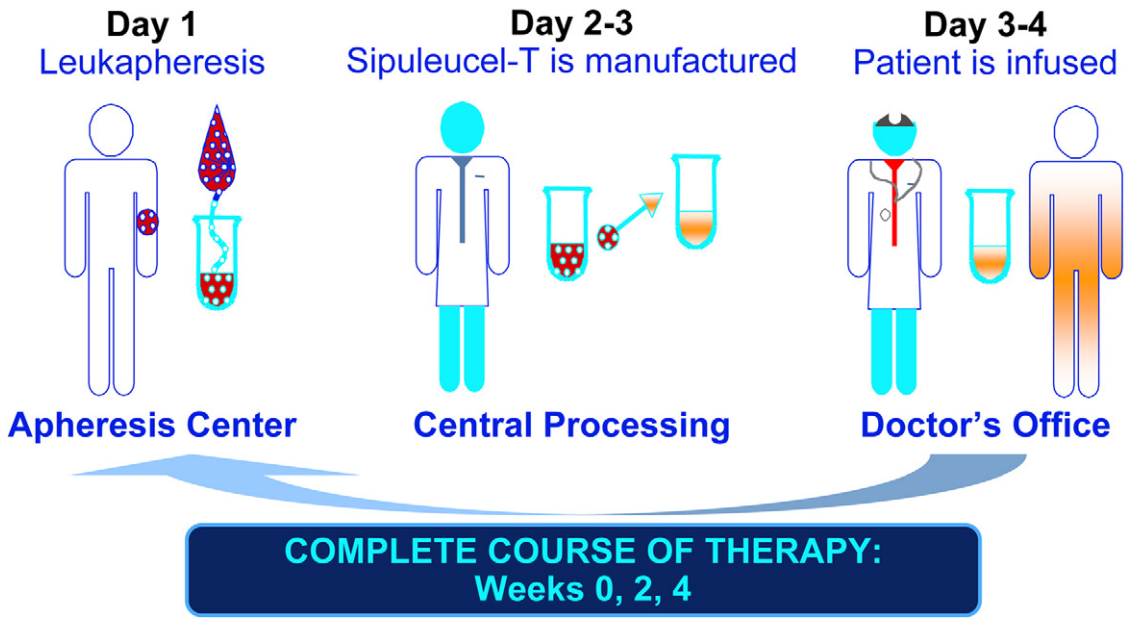

Fig. 3. Logistics of therapy with sipleucel-T. Reprinted with permission from Dendreon [from PROVENGE® (sipuleucel-T) Cellular, Tissue, and Gene Therapies Advisory Committee Meeting March 29, 2007. The Mattson Jack Group, Cancer Metric Database 2009].

2007, but more data were requested. In both studies, the primary endpoint was progression, not OS, and the FDA wanted evidence that the primary endpoint was met.

These results led to a larger phase 3 study, IMPACT (Immunotherapy Prostate AdenoCarcinoma Treatment), which enrolled 512 men with asymptomatic or minimally symptomatic CRPC [13]. The main difference between this and prior trials was the selection of OS, not TTP, as the primary endpoint. As in the previous studies, patients were randomly assigned in a 2:1 fashion to receive either the vaccine or placebo, and patients were allowed to cross over to a frozen version of the vaccine at disease progression if they had received placebo initially. (Cells were processed and frozen away, and at the time of disease progression, thawed and given to the patient.) Approximately 50% of patients on the control arm received the vaccine at the time of progression.

The results of this study mirrored the results of prior smaller studies in demonstrating a difference in median survival of 4.1 months with a 36.5-month median follow-up (hazard ratio (HR) = 0.76; 95% CI, 0.61–0.95; $P = 0.02$ (Cox model). The proportion of patients who were alive at 3 years was 38% higher with sipuleucel-T than with placebo. Based on these data, the FDA approved sipuleucel-T for treatment of asymptomatic or minimally symptomatic mCRPC in 2010.

Additional data analysis, in the form of a Forest plot (Fig. 4), showed that virtually every subset of patients benefited from the vaccination strategy, including those with Gleason score 4 or above or 3 or below, bone metastases (less than 10 vs. 10 or greater), ECOG status (0 or 1), age above or below the median, and PSA activity above or below the median. Unlike the results of the Small study, however, TTP did not differ between the treatment arms; median time to progression in the placebo arm was 14.4 weeks vs. 14.6 in the sipuleucel-T arm (HR = 0.951, 95% CI, 0.77–1.17; $P = 0.63$ log-rank). The protocol did not require that further details about disease be collected systematically after disease progression; therefore, it remains speculative about whether the pace of the disease was slowed by sipuleucel-T. However, given the survival benefit, it is likely that there was some attenuation of the disease that was not measured in the trial. The only indication of a possible effect on disease progression effect came after 6 months of therapy, in the subgroup of patients that was asymptomatic at baseline.

Additional studies performed during this trial considered more specifically the question of how the immune system might be activated by sipuleucel-T [15–18]. An evaluation of the activation of different components of the immune system determined that APCs in the product are indeed activated by the exposure to the fusion antigen at 0, 2, and 4 weeks after initiation of therapy [16]. In addition, sipuleucel-T generated cytokine production and persistent, antigen-specific humoral responses to PA2024 (the fusion antigen) and PAP [15]. These results do not necessarily indicate that the vaccine is working by means of producing antibodies; they do serve as markers of immune system activation. A correlation was also noted between activation of humoral response or antibody production

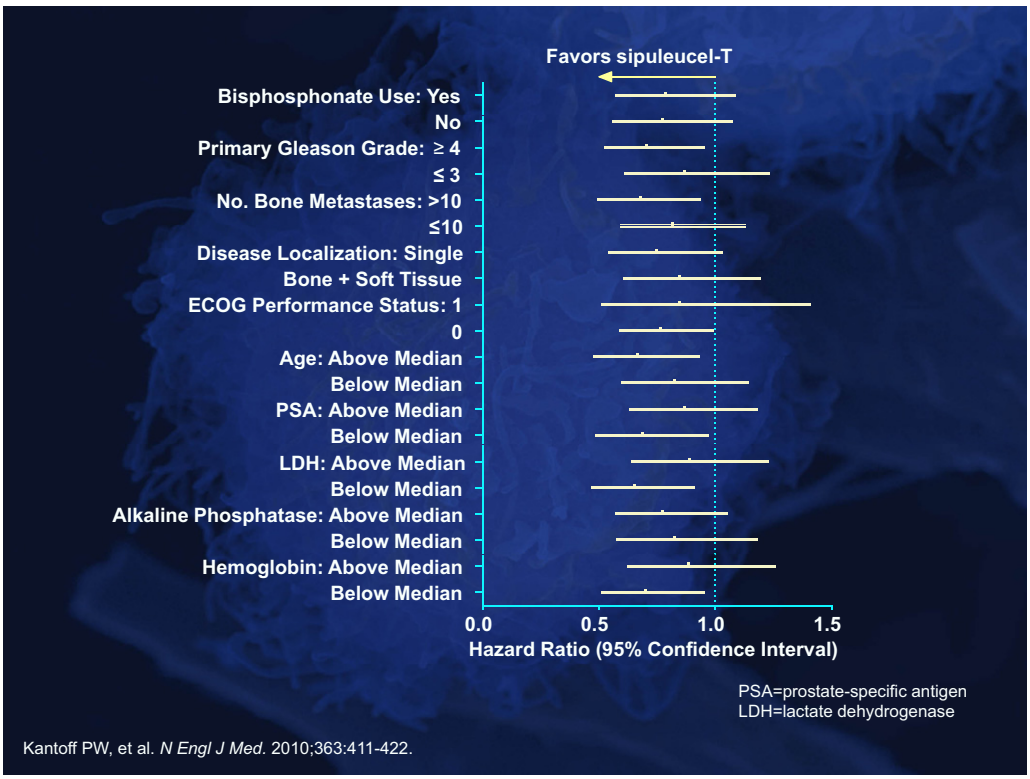

Fig. 4. Forest plot showing consistent survival effect across subpopulations. PSA, prostate-specific antigen; LDH, lactate dehydrogenase. Adapted with permission from Massachusetts Medical Society ©2010 [13].

and overall survival; that is, the more antibody that was produced, the greater the likelihood that a patient lived longer. This again indicates a stimulation of the immune system, and it suggests that stimulation of the immune system makes a difference and correlates with overall outcome.

Adverse events were modest in the sipuleucel-T arm and included primarily chills, fever, headache, flu-like illness, myalgia, and hypertension. Most occurred during a 24-hour period and responded to treatment with acetaminophen.

Patients should be informed that PSA will not likely decline, and that no clinically apparent changes take place. Patients' clinical status does not usually change. After treatment with sipuleucel-T, patients should receive additional therapies as otherwise indicated.

Additional practical issues must be considered when using sipuleucel-T in the clinical setting. The FDA-approved indication is for men with mCRPC who are asymptomatic or minimally symptomatic. Sipuleucel-T should be prescribed early in the course of mCRPC, ideally before numerous second-line hormone treatments are given. The best patients for therapy with sipuleucel-T are probably those who have newly diagnosed CRPC and a relatively slow PSA doubling time. The patients are likely to have no or minimal symptoms due to bone metastases, and the immune system is more robust. Sipuleucel-T should be given before corticosteroid use with chemotherapy and/or abiraterone. Furthermore, these patients are less likely to have liver metastases, which usually portend a very poor prognosis and short survival. Sipuleucel-T should only be given in select patients after chemotherapy. Physicians should consider whether the patient is on steroids, and, if so, whether the steroids can be stopped or tapered without causing a pain flare.

Medicare and private insurance reimbursement issues are now much clearer than they were initially. All Medicare Administrative Contractor regions are required to cover sipuleucel-T based on the FDA-approved label according to the National Coverage Decision (NCD) issued on July 8, 2011 by the Centers for Medicare and Medicaid Services (CMS) (Transmittal 2254) [19]. Insurance plans representing approximately 99% of patients with private insurance also cover sipuleucel-T for the FDA-approved indication.

Experience with sipuleucel-T in patients with mCRPC has led to the realization that some patients develop pain after the first or second infusion, and the source can be difficult to ascertain unless the patient has had baseline imaging before initiating this treatment. Patients should be checked monthly for symptomatic progression, and imaging should be repeated 3 months after treatment is begun.

When considering the sequence of FDA-approved agents in mCRPC, sipuleucel-T should be used early in the spectrum of disease, probably followed by chemotherapy. Abiraterone and cabazitaxel are now approved for use after docetaxel. MDV3100 and radium-223 are likely to become additional FDA-approved options in the next year or so. Assuming these are approved, some confusion will occur over which of these to give first and when. Other agents are being studied in clinical trials and may become available as well. The optimal sequencing of agents in mCRPC has now become a very challenging area, not only for researchers, but for all physicians treating these patients.

Ipilimumab

CTLA-4 has been shown to be a potent negative regulator of T cell activation [8]. Researchers suspected this attribute could be exploited as a part of a very powerful approach generating an immune response against tumor cells. Ipilimumab, an antibody to CTLA-4, blocks CTLA-4 activity, and produces a very robust activation of T cells against tumors. It has been approved for use in patients with another solid tumor, melanoma, based on data from two phase 3 clinical trials [20,21].

Results from a preclinical study indicated that radiation augments CTLA-4 blockade [22], which led to the design of a phase 1–2 trial of ipilimumab in mCRPC. Ipilimumab was given alone in a dose-escalation portion of the study and then with the addition of a single fraction of radiation each day before starting ipilimumab [23,24]. The treatment resulted in some very significant PSA declines.

Currently, two phase 3 programs are evaluating ipilimumab for the treatment of mCRPC, both in asymptomatic or minimally symptomatic patients who have not received docetaxel and also in patients with bone metastases who have already completed docetaxel treatment. The trial participants who have received docetaxel are treated with either a single fraction of radiation or a single fraction of radiation plus ipilimumab. The asymptomatic or minimally symptomatic enrollees are treated either with placebo or ipilimumab alone. In both trials, overall survival is the primary endpoint.

PROSTVAC-VF-TRICOM

Another immunotherapeutic strategy, developed at the National Institutes of Health by Schlom uses genetically engineered highly immunogenic poxviruses in which the tumor antigen PSA was inserted along with 3 co-stimulatory molecules [25]. PROSTVAC-VF-TRICOM is based on a combination of 2 viral particles, vaccinia, which is given first, followed by fowlpox. Vaccinia is a potent immunologic priming agent. Fowlpox, which is minimally or non-cross reactive with vaccinia, is used as a boosting agent. Both are genetically engineered to contain a slightly modified PSA transgene altered to increase immunogenicity and increase HLA-A2 binding. PROSTVAC-VF-TRICOM also contains 3 immunogenic molecules, which are presumably secreted by the poxvirus, lymphocyte function-associated antigen 3 (LFA-3), intracellular adhesion molecule (ICAM), and a co-stimulatory molecule for T cells (B.1), each of which specifically stimulate the immune system.

PROSTVAC-VF-TRICOM was evaluated in a randomized phase 2 clinical trial to determine whether it prolonged

time to disease progression in men with mCRPC [26]. A total of 125 men with asymptomatic or minimally symptomatic mCRPC were randomly assigned in a 2:1 fashion to receive the PROSTVAC-VF-TRICOM or empty vector plus placebo. Those who received PROSTVAC-VF-TRICOM also received GM-CSF at the same time. The primary endpoint in this study was progression-free survival (PFS). At the time of disease progression, patients were allowed to cross over to the vaccine arm if they had been receiving the placebo. Patients were followed until death. OS was the secondary endpoint.

Men with either minimally symptomatic or asymptomatic mCRPC progressed very quickly. PFS did not differ between the 2 trial arms (control, median 3.7 months; PROSTVAC-VF-TRICOM, median 3.8 months; HR 0.88; 95% CI 0.57–1.38; $P = 0.60$). Theoretically, however, these vaccines might take months to provide optimal immunization.

The trial provided positive results in OS, with a difference of 8 months between treatment groups. Median OS in the control group was 16.6 vs. 25.1 months in the PROSTVAC-VF-TRICOM group (HR = 0.56, 95% CI 0.37–0.85; $P = 0.006$). This was an exciting but preliminary result that led to the design of a global phase 3 trial of PROSTVAC-VF-TRICOM that opened recently. In the PROSPECT trial, 1,200 men with asymptomatic or minimally symptomatic mCRPC will be randomly assigned to receive either a vector placebo plus adjuvant placebo without GM-CSF, PROSTVAC-VF-TRICOM without GM-CSF (which was given in the phase 2 trial), or PROSTVAC-VF-TRICOM plus GM-CSF. Patients will be followed to determine survival, and the primary endpoint is OS.

GVAX

GVAX pancreatic cancer vaccine is a cellular-based therapy that has been tested in a randomized phase 3 study. Allogeneic PCA cell lines were transfected with GM-CSF and the cells were radiated. The lysates were used as immune stimulants of dendritic cells, the APCs. The in vitro experiments in animals were very promising, as were some early clinical trials. Simons presented some early data showing GVAX truncated the rise in patients' PSA values, suggesting clinical benefit [27].

To develop GVAX, lysates were created from 2 PCA cell lines, LNCaP and PC3, which had been transfected with GM-CSF [28]. Dendritic cells exposed to the lysates became activated and, in turn, activated T cells. The mechanism of action of GVAX is presumed to be that of a dendritic cell vaccine, which led GVAX to become the first such vaccine tested in a clinical trial. In practice, a patient receives 6 injections in each leg, 12 injections at a time, and the treatments are repeated every 3 weeks. The injection sites redden, presumably demonstrating an immunologic response to vaccination.

Two-phase 3 trials of GVAX were conducted several years ago, Vaccine Immunotherapy with Allogenic Prostate Cancer Cell line 1 (VITAL-1) and VITAL-2 [29]. VITAL-2 studied patients with symptomatic mCRPC who were eligible to receive docetaxel. Patients were randomized to receive docetaxel or docetaxel plus GVAX. At a planned interim analysis, there were more deaths in the experimental arm and the Data and Safety Monitoring Board (DSMB) recommended study closure based on safety concerns.

VITAL-1 enrolled men with mCRPC who were asymptomatic and randomly assigned them to vaccine or docetaxel. At the time of disease progression, patients were treated according to clinician choice, so that patients receiving GVAX could receive docetaxel. Patients who progressed on chemotherapy were not permitted to receive GVAX. Although there was no adverse safety signal observed in VITAL-1, a futility analysis was done after VITAL-2 was closed. Because the futility analysis suggested that there was less than a 20% chance the trial would be positive, VITAL-1 was closed as well, and Cell Genesys, the manufacturer of this product, was closed. Johns Hopkins is currently studying the GVAX platform in other solid tumors.

Conclusions

In addition to sipuleucel-T, cabazitaxel and abiraterone have been approved by the FDA for use after docetaxel. The results of MDV3100, now called enzalutamide, in the AFFIRM trial, showed survival benefit over placebo after docetaxel, and this agent is likely to gain approval in 2012 [30]. The ASLYMPCA trial studied men with symptomatic mCRPC who had either received prior docetaxel or who were "unsuitable" to received docetaxel. Men who received radium-223 had improved survival over standard of care [31], and this agent is also likely to receive FDA approval in the coming year. The COU 302 trial of abiraterone and prednisone before docetaxel extends progression-free survival, but overall survival data are pending [32]. Sequencing of these new agents after sipuleucel-T will be actively studied in future trials. The optimal sequencing of all of these active agents remains to be clarified. It is hoped that development of biomarkers will better inform the sequencing for a given patient.

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Statement of Conflicts of Interest

Philip Kantoff, MD, has disclosed the following relevant financial relationships whose products or services may be mentioned in this activity: He is a Consultant/Advisor for

Progenics Pharmaceuticals, Amgen USA, Tokai, BN Immunotherapeutics, Ortho Biotech, Belicum, Genentech, and Johnson & Johnson Scientific Advisory. He is on the Board of Bind Biosciences, Inc and receives grant support from Celgene, Milenium, and Oncogenex.

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