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Highlights in Prostate Cancer From the 2011 American Urological Association Annual Meeting and the 2011 American Society of Clinical Oncology Annual Meeting

Reporting on:

- Immunotherapy for Early Treatment of Advanced Prostate Cancer
- New Insights into the Androgen Receptor and ERG in Prostate Cancer
- Castrate-Resistant Prostate Cancer—New Therapeutic Approaches
- Circulating Tumor Cells in Prostate Cancer
- Prostate-Specific Antigen Kinetics in the Management of Prostate Cancer

PLUS Meeting Abstract Summaries

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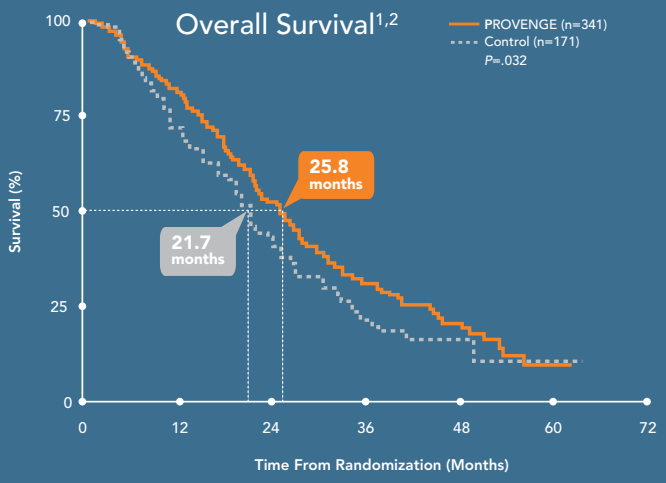
In asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer

PROVENGE is the first in a new class of therapy that is designed to activate a patient's own antigen-presenting cells to stimulate an immune response against prostate cancer.

- **Extends median survival beyond 2 years**—25.8 months compared with 21.7 months for patients in the control* group (*P*=.032)
- **Reduction in risk of death—22.5%** (HR=0.775, 95% CI: 0.614, 0.979)
- **Therapy completed in 3 cycles**—3 infusions, at approximately 2-week intervals†
- **Most common adverse events are primarily mild or moderate**—chills, fatigue, fever, back pain, nausea, joint ache, and headache



Data originally published in the *New England Journal of Medicine*: Kantoff PW, Higano CS, Shore ND, et al; for the IMPACT Study Investigators. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med*. 2010;363:411-422.

INDICATION: PROVENGE® (sipuleucel-T) is an autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.

IMPORTANT SAFETY INFORMATION: PROVENGE is intended solely for autologous use and is not routinely tested for transmissible infectious diseases.

In controlled clinical trials, serious adverse events reported in the PROVENGE group include acute infusion reactions (occurring within 1 day of infusion) and cerebrovascular events. Severe (Grade 3) acute infusion reactions were reported in 3.5% of patients in the PROVENGE group. Reactions included chills, fever, fatigue, asthenia, dyspnea, hypoxia, bronchospasm, dizziness, headache, hypertension, muscle ache, nausea, and vomiting. No Grade 4 or 5 acute infusion reactions were reported in patients in the PROVENGE group.

The most common adverse events (incidence ≥15%) reported in the PROVENGE group are chills, fatigue, fever, back pain, nausea, joint ache, and headache.

Please see Brief Summary of full Prescribing Information on the adjacent page.

*Control was nonactivated, autologous, peripheral blood mononuclear cells.
†The dosing interval ranged from 1 to 15 weeks in controlled clinical trials.

1. PROVENGE [package insert]. Dendreon Corporation; April 2010.
2. Kantoff PW, Higano CS, Shore ND, et al; for the IMPACT Study Investigators. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med*. 2010;363:411-422.

Dendreon
Targeting Cancer, Transforming Lives®

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PROVENGE®
(sipuleucel-T)
Stimulate a Response

PROVENGE® (sipuleucel-T)
Suspension for Intravenous Infusion **Rx Only**

BRIEF SUMMARY – See full Prescribing Information for complete product information

INDICATIONS AND USAGE: PROVENGE® (sipuleucel-T) is an autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.

DOSAGE AND ADMINISTRATION

- **For Autologous Use Only.**
- The recommended course of therapy for PROVENGE is 3 complete doses, given at approximately 2-week intervals.
- Premedicate patients with oral acetaminophen and an antihistamine such as diphenhydramine.
- Before infusion, confirm that the patient's identity matches the patient identifiers on the infusion bag.
- **Do Not Initiate Infusion of Expired Product.**
- Infuse PROVENGE intravenously over a period of approximately 60 minutes. **Do Not Use a Cell Filter.**
- Interrupt or slow infusion as necessary for acute infusion reactions, depending on the severity of the reaction.

(See Dosage and Administration [2] of full Prescribing Information.)

CONTRAINDICATIONS: None.

WARNINGS AND PRECAUTIONS

- **PROVENGE is intended solely for autologous use.**
- **Acute infusion reactions** (reported within 1 day of infusion) included, but were not limited to, fever, chills, respiratory events (dyspnea, hypoxia, and bronchospasm), nausea, vomiting, fatigue, hypertension, and tachycardia. In controlled clinical trials, 71.2% of patients in the PROVENGE group developed an acute infusion reaction.

  In controlled clinical trials, severe (Grade 3) acute infusion reactions were reported in 3.5% of patients in the PROVENGE group. Reactions included chills, fever, fatigue, asthenia, dyspnea, hypoxia, bronchospasm, dizziness, headache, hypertension, muscle ache, nausea, and vomiting. The incidence of severe events was greater following the second infusion (2.1% vs 0.8% following the first infusion), and decreased to 1.3% following the third infusion. Some (1.2%) patients in the PROVENGE group were hospitalized within 1 day of infusion for management of acute infusion reactions. No Grade 4 or 5 acute infusion reactions were reported in patients in the PROVENGE group.

  Closely monitor patients with cardiac or pulmonary conditions. In the event of an acute infusion reaction, the infusion rate may be decreased, or the infusion stopped, depending on the severity of the reaction. Appropriate medical therapy should be administered as needed.
- **Handling Precautions for Control of Infectious Disease.** PROVENGE is **not** routinely tested for transmissible infectious diseases. Therefore, patient leukapheresis material and PROVENGE may carry the risk of transmitting infectious diseases to health care professionals handling the product. Universal precautions should be followed.
- **Concomitant Chemotherapy or Immunosuppressive Therapy.** Use of either chemotherapy or immunosuppressive agents (such as systemic corticosteroids) given concurrently with the leukapheresis procedure or PROVENGE has not been studied. PROVENGE is designed to stimulate the immune system, and concurrent use of immunosuppressive agents may alter the efficacy and/or safety of PROVENGE. Therefore, patients should be carefully evaluated to determine whether it is medically appropriate to reduce or discontinue immunosuppressive agents prior to treatment with PROVENGE.
- **Product Safety Testing.** PROVENGE is released for infusion based on the microbial and sterility results from several tests: microbial contamination determination by Gram stain, endotoxin content, and in-process sterility with a 2-day incubation to determine absence of microbial growth. The final (7-day incubation) sterility test results are not available at the time of infusion. If the sterility results become positive for microbial contamination after PROVENGE has been approved for infusion, Dendreon will notify the treating physician. Dendreon will attempt to identify the microorganism, perform antibiotic sensitivity testing on recovered microorganisms, and communicate the results to the treating physician. Dendreon may request additional information from the physician in order to determine the source of contamination.

(See Warnings and Precautions [5] of full Prescribing Information.)

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety evaluation of PROVENGE is based on 601 prostate cancer patients in the PROVENGE group who underwent at least 1 leukapheresis procedure in four randomized, controlled clinical trials. The control was non-activated autologousperipheral blood mononuclear cells.

The most common adverse events, reported in patients in the PROVENGE group at a rate ≥15%, were chills, fatigue, fever, back pain, nausea, joint ache, and headache. Severe (Grade 3) and life-threatening (Grade 4) adverse events were reported in 23.6% and 4.0% of patients in the PROVENGE group compared with 25.1% and 3.3% of patients in the control group. Fatal (Grade 5) adverse events were reported in 3.3% of patients in the PROVENGE group compared with 3.6% of patients in the control group.

Serious adverse events were reported in 24.0% of patients in the PROVENGE group and 25.1% of patients in the control group. Serious adverse events in the PROVENGE group included acute infusion reactions *(see Warnings and Precautions)*, cerebrovascular events, and single case reports of eosinophilia, rhabdomyolysis, myasthenia gravis, myositis, and tumor flare.

PROVENGE was discontinued in 1.5% of patients in Study 1 (PROVENGE group n=341; Control group n=171) due to adverse events. Some patients who required central venous catheters for treatment with PROVENGE developed infections, including sepsis. A small number of these patients discontinued treatment as a result. Monitoring for infectious sequelae in patients with central venous catheters is recommended.

Each dose of PROVENGE requires a standard leukapheresis procedure approximately 3 days prior to the infusion. Adverse events that were reported ≤1 day following a leukapheresis procedure in ≥5% of patients in controlled clinical trials included citrate toxicity (14.2%), oral paresthesia (12.6%), paresthesia (11.4%), and fatigue (8.3%).

Table 1 provides the frequency and severity of adverse events reported in ≥5% of patients in the PROVENGE group of randomized, controlled trials of men with prostate cancer. The population included 485 patients with metastatic castrate resistant prostate cancer and 116 patients with non-metastatic androgen dependent prostate cancer who were scheduled to receive 3 infusions of PROVENGE at approximately 2-week intervals. The population was age 40 to 91 years (median 70 years), and 90.6% of patients were Caucasian.

Table 1 Incidence of Adverse Events Occurring in ≥5% of Patients Randomized to PROVENGE

	PROVENGE (N = 601)		Control* (N = 303)	
	All Grades n (%)	Grade 3-5 n (%)	All Grades n (%)	Grade 3-5 n (%)
Any Adverse Event	**591 (98.3)**	**186 (30.9)**	**291 (96.0)**	**97 (32.0)**
Chills	319 (53.1)	13 (2.2)	33 (10.9)	0 (0.0)
Fatigue	247 (41.1)	6 (1.0)	105 (34.7)	4 (1.3)
Fever	188 (31.3)	6 (1.0)	29 (9.6)	3 (1.0)
Back pain	178 (29.6)	18 (3.0)	87 (28.7)	9 (3.0)
Nausea	129 (21.5)	3 (0.5)	45 (14.9)	0 (0.0)
Joint ache	118 (19.6)	11 (1.8)	62 (20.5)	5 (1.7)
Headache	109 (18.1)	4 (0.7)	20 (6.6)	0 (0.0)
Citrate toxicity	89 (14.8)	0 (0.0)	43 (14.2)	0 (0.0)
Paresthesia	85 (14.1)	1 (0.2)	43 (14.2)	0 (0.0)
Vomiting	80 (13.3)	2 (0.3)	23 (7.6)	0 (0.0)
Anemia	75 (12.5)	11 (1.8)	34 (11.2)	7 (2.3)
Constipation	74 (12.3)	1 (0.2)	40 (13.2)	3 (1.0)
Pain	74 (12.3)	7 (1.2)	20 (6.6)	3 (1.0)
Paresthesia oral	74 (12.3)	0 (0.0)	43 (14.2)	0 (0.0)
Pain in extremity	73 (12.1)	5 (0.8)	40 (13.2)	1 (0.3)
Dizziness	71 (11.8)	2 (0.3)	34 (11.2)	0 (0.0)
Muscle ache	71 (11.8)	3 (0.5)	17 (5.6)	0 (0.0)
Asthenia	65 (10.8)	6 (1.0)	20 (6.6)	2 (0.7)
Diarrhea	60 (10.0)	1 (0.2)	34 (11.2)	3 (1.0)
Influenza-like illness	58 (9.7)	0 (0.0)	11 (3.6)	0 (0.0)
Musculoskeletal pain	54 (9.0)	3 (0.5)	31 (10.2)	3 (1.0)
Dyspnea	52 (8.7)	11 (1.8)	14 (4.6)	3 (1.0)
Edema peripheral	50 (8.3)	1 (0.2)	31 (10.2)	1 (0.3)
Hot flush	49 (8.2)	2 (0.3)	29 (9.6)	1 (0.3)
Hematuria	46 (7.7)	6 (1.0)	18 (5.9)	3 (1.0)
Muscle spasms	46 (7.7)	2 (0.3)	17 (5.6)	0 (0.0)

(Table 1 continued on next page.)

Table 1 Incidence of Adverse Events Occurring in ≥5% of Patients Randomized to PROVENGE

	PROVENGE (N = 601)		Control* (N = 303)	
	All Grades n (%)	Grade 3-5 n (%)	All Grades n (%)	Grade 3-5 n (%)
Hypertension	45 (7.5)	3 (0.5)	14 (4.6)	0 (0.0)
Anorexia	39 (6.5)	1 (0.2)	33 (10.9)	3 (1.0)
Bone pain	38 (6.3)	4 (0.7)	22 (7.3)	3 (1.0)
Upper respiratory tract infection	38 (6.3)	0 (0.0)	18 (5.9)	0 (0.0)
Insomnia	37 (6.2)	0 (0.0)	22 (7.3)	1 (0.3)
Musculoskeletal chest pain	36 (6.0)	2 (0.3)	23 (7.6)	2 (0.7)
Cough	35 (5.8)	0 (0.0)	17 (5.6)	0 (0.0)
Neck pain	34 (5.7)	3 (0.5)	14 (4.6)	2 (0.7)
Weight decreased	34 (5.7)	2 (0.3)	24 (7.9)	1 (0.3)
Urinary tract infection	33 (5.5)	1 (0.2)	18 (5.9)	2 (0.7)
Rash	31 (5.2)	0 (0.0)	10 (3.3)	0 (0.0)
Sweating	30 (5.0)	1 (0.2)	3 (1.0)	0 (0.0)
Tremor	30 (5.0)	0 (0.0)	9 (3.0)	0 (0.0)

*Control was non-activated autologous peripheral blood mononuclear cells.

Cerebrovascular Events. In controlled clinical trials, cerebrovascular events, including hemorrhagic and ischemic strokes, were reported in 3.5% of patients in the PROVENGE group compared with 2.6% of patients in the control group.

(See Adverse Reactions [6] of full Prescribing Information.)

To report SUSPECTED ADVERSE REACTIONS, contact Dendreon Corporation at 1-877-336-3736 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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PROVENGE®
(sipuleucel-T)

Immunotherapy for Early Treatment of Advanced Prostate Cancer

At the 2011 American Urological Association (AUA) meeting, Dr. Paul Schellhammer discussed immunotherapy for early treatment of advanced prostate cancer.[1] Just 15 years ago, when men developed metastatic prostate disease that was detected clinically by imaging, they were given androgen deprivation therapy (ADT). Currently, ADT is used for patients who have a rising prostate-specific antigen (PSA) level without any imaging abnormalities.

In the asymptomatic patient who has a good quality of life, there has been a tendency to delay imaging investigations because, up until now, there was little that one would do in the absence of symptoms. The asymptomatic and minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC) disease state has become largely overlooked and underdiagnosed in the absence of a therapy that could make a difference for the patient. However, for these patients, it is now becoming increasingly important to detect the disease state before it becomes symptomatic, in order to allow for the use of the immunotherapy sipuleucel-T, according to its indicated label and under conditions in which the treatment has proven beneficial in clinical trials. Therefore, imaging studies are now more important than ever, in order to identify patients in the asymptomatic and minimally symptomatic but metastatic stage.

One of the more attractive characteristics of sipuleucel-T is the relatively well tolerated safety profile; it is associated with very few adverse events. This profile appears to be a characteristic of this class of agents, though it cannot be considered a blanket statement. For example, the monoclonal antibody ipilimumab can cause autoimmune disease. Therefore, immunotherapy does not automatically translate to a low toxicity profile.

One question raised during this presentation was regarding the incorporation of sipuleucel-T together with chemotherapy in the overall patient treatment strategy. Emerging evidence now points to the possibility that chemotherapy and immunotherapy may in fact be complementary therapies. Although the optimal sequencing has yet to be determined, it is certain that chemotherapy generates a general "danger signal" that will act as an immune stimulant. If the immune system has been properly programmed, it is beneficial in that regard. Chemotherapy can unmask antigens as a result of cell death, resulting in the phenomenon of epitope spreading. There is also evidence that some of the regulatory cells can be downsized, which again takes the hold off the immune system and might accelerate a favorable immune response.

ABSTRACT SUMMARY A Randomized, Controlled Phase III Global Trial Comparing Sipuleucel-T Plus Androgen Deprivation Therapy Versus Androgen Deprivation Therapy Alone in Men With Metastatic Androgen Dependent (Hormone Sensitive) Prostate Cancer

Fizazi and coworkers plan to enroll 1,684 patients with metastatic androgen-dependent prostate cancer in a randomized, open-label, multicenter, global trial that will assess the efficacy of sipuleucel-T in this patient population (ASCO Abstract TPS188). The primary endpoint is OS; secondary endpoints are safety, quality of life, time to castration resistance, and chemotherapy-free survival. ADT will be administered to patients in order to achieve castration-level testosterone. Following ADT, patients will be randomized in a 1:1 fashion to receive either sipuleucel-T or continue on ADT alone. The Prostate Cancer Working Group 2 guidelines will be utilized in order to determine castration resistance. A subpopulation of 600 patients from the study will be used to evaluate pharmacodynamic measures, including serum and blood samples for cellular and humoral immune response analyses, as well as CTC. The study investigators also hope to further elucidate their understanding of the immunological response and clinical benefits of sipuleucel-T.

Reference

1. Schellhammer P. Immunotherapy for Early Treatment of Advanced Prostate Cancer. Paper presented at the 2011 Annual Meeting of the American Urological Association; May 14-19, 2011; Washington, DC.

The Androgen Receptor and ERG in Prostate Cancer

Dr. Charles Sawyer discussed the androgen receptor and ERG in prostate cancer at the AUA meeting.[1] Several points within the androgen receptor signaling pathway have been exploited for targeted therapy in mCRPC. For example, luteinizing hormone-releasing hormone agonists inhibit the production of testosterone hormone and thereby prevent testosterone-induced androgen receptor activation, while anti-androgens target the androgen receptor itself. In 2004, Chen and colleagues published a critical paper which provided insight into the primary mechanism of resistance to castration and current antiandrogen therapy.[2] These researchers demonstrated that the androgen receptor is overexpressed in castration-resistant sublines of multiple prostate cancer xenograft models, as well as in patients who are classified as castration-resistant. Further, forced overexpression of the androgen receptor confers castration resistance, whereas androgen receptor knockdown impairs castration-resistant growth.

Interestingly, when androgen receptor levels are high, androgen receptor antagonists act instead as agonists. Therefore, Jung and colleagues recently published a cell-based structure-activity relationship screening study that was conducted on a series of thiohydantoins and their analogues.[3] Using both crystal structure as well as homology modeling and binding affinities, compounds with greater antagonism but no agonism (ie, pure antagonists) were sought in particular. This study led to the discovery of MDV3100 as a clinical candidate for the treatment of CRPC.

MDV3100 was evaluated in a phase I/II multicenter first-in-man trial in CRPC.[3] This study was conducted in 5 US centers in 140 patients with progressive mCRPC. Patients were enrolled in dose-escala-

ABSTRACT SUMMARY **Abiraterone Acetate in Patients With Metastatic Castration-Resistant Prostate Cancer and Prior Therapy With Ketoconazole: A Prostate Cancer Clinical Trials Consortium Study**

The main objective of this phase II study from Ryan and colleagues (ASCO Abstract 4500) was to determine the efficacy of abiraterone in patients with disease progression on ketoconazole, in order to provide clinical data regarding the potential for sequencing of these 2 agents. All patients had mCRPC and had received prior ketoconazole for more than 28 days; prior chemotherapy was not permitted. Patients had evidence of either progression on ketoconazole, or had experienced prior grade 3/4 adverse events on ketoconazole. At the time of this report, 16 patients (median age: 72.5 years, range: 52–93 years) had been enrolled. The median PSA at baseline was 62.5 ng/dL (range: 2.1–922.4 ng/dL), and patients had metastases to either bone (n=15) or soft tissue (n=6). At baseline, all patients were shown to have adequate adrenal function, suggesting that prior ketoconazole therapy did not result in permanent adrenal dysfunction. Of the 16 patients enrolled, 13 had completed 12 weeks of therapy. After 12 weeks on abiraterone therapy, 21% (95% CI, 5–51) and 42% (95% CI, 18–71) of 14 patients experienced a 50% or greater decline or a 30% or greater decline in PSA, respectively. The adverse events observed were similar to those previously reported with abiraterone, but do reflect the more progressive disease of the patients in this study as compared with prior abiraterone clinical trials.

ABSTRACT SUMMARY MDV3100 Effects On Androgen Receptor (AR) Signaling and Bone Marrow Testosterone Concentration Modulation: A Preliminary Report

Efstathiou and colleagues tested the hypothesis that the efficacy of MDV-3100 in mCRPC was associated with its ability to inhibit androgen signaling (ASCO Abstract 4501). The primary study endpoint was to determine any effect of MDV3100 on androgen signaling, and correlate molecular changes at baseline and follow-up with any clinical phenotype. In addition to CYP17 expression and testosterone levels in the bone marrow, other biomarkers included subcellular expression of the androgen receptor and Src kinase activity, which has been shown to interface with the androgen receptor pathway. Enrolled patients (N=58) received MDV3100 (160 mg daily) and underwent blood work and bone marrow biopsy at baseline, week 8 of treatment, and upon study discontinuation. Patients who became symptomatic or displayed progression upon imaging were taken off-study. MDV3100 was well tolerated, with the most common adverse events being grade 1/2 fatigue (24%), anorexia (16%), and nausea/vomiting (9%). Following MDV3100 treatment, 55%, 45%, and 20% of evaluable patients (N=55) experienced a 30% or greater, 50% or greater, or 90% or greater PSA reduction, respectively. The mean CYP17 expression was significantly higher in patients who achieved a 50% or greater PSA decline versus patients who did not (70% vs 10%; *P*=.002), as was the mean testosterone levels in the bone marrow aspirate (0.033 vs 0.016; *P*=.019).

tion cohorts of 3–6 patients each. All patients received an initial daily starting dose of 30 mg MDV3100. Final daily MDV3100 doses were 30 mg (n=3), 60 mg (n=27), 150 mg (n=28), 240 mg (n=29), 360 mg (n=28), 480 mg (n=22), and 600 mg (n=3).

MDV3100 doses from 60–480 mg daily showed effective androgen receptor blockade, evidenced by decreased (18) F-fluoro-5alpha-dihydrotestosterone binding imaged on positron emission tomography (PET). Other endpoints included median time to progression (47 weeks, 95% confidence interval [CI], 34–not reached), and maximum tolerated dose (240 mg) for sustained treatment (>28 days). The most common grade 3/4 adverse event was dose-dependent fatigue (11% patients), which was generally resolved after dose reduction.

Antitumor activity was attributed to all doses of MDV3100, including decreases of at least 50% in PSA (56%), responses in soft tissue (22%), stabilized bone disease (56%), and conversion from unfavorable to favorable circulating tumor cell counts (49%).

More patients who were chemotherapy-naïve achieved a decline in PSA of at least 50%, compared with patients who had received prior chemotherapy (62% vs 51%). One potential mechanism to explain the resistance shown by some patients to MDV3100 is loss of the tumor suppressor PTEN, a negative regulator of the PI3K pathway. PTEN loss is common in prostate cancer, occurring in approximately 40% of patients. Indeed, when a PTEN-knockout animal model was treated with MDV3100, it was found to be minimally effective in both reduction of tumor volume as well as decreased mRNA levels of androgen receptor target genes. Further preclinical work showed that the androgen receptor pathway is connected to the PI3K/PTEN pathway through negative feedback loops, whereby inhibition of one pathway activates the other pathway. Thus, inhibition of the PI3K pathway is hypothesized to result in disease stabilization without an overt tumor response. For this reason, PSA may not be an effective endpoint to use in clinical trials of PI3K inhibitors.

In 2010, Park and colleagues reported a study of a specific anti-ERG antibody in prostate cancer.[4] TMPRSS2-ERG gene fusions are a relatively common event in prostate cancer that result in the production of a truncated ERG protein product. Using a unique antibody that detects this truncated ERG protein, Park and colleagues found an association between ERG gene rearrangement and truncated ERG protein product expression. Other laboratory studies of ERG function have now established that ERG expression causes downregulation of terminal differentiation genes (including EZH2 in prostate cancer[5]), and that the ERG transcriptome is actually reminiscent of squamous skin cancer. In the ventral prostate, ectopic ERG induces hyperplasia, and in PTEN-null prostate tumors, ERG actually induces invasive prostate cancer.

References

1. Sawyer CL. New Insights into Androgen Receptor and ERG in Prostate Cancer. Paper presented at the 2011 Annual Meeting of the American Urological Association; May 14-19, 2011; Washington, DC.
2. Chen CD, Welsbie DS, Tran C, et al. Molecular determinants of resistance to antiandrogen therapy. *Nat Med.* 2004;1:33-39.
3. Jung ME, Ouk S, Yoo D, et al. Structure-activity relationship for thiohydantoin androgen receptor antagonists for castration-resistant prostate cancer (CRPC). *J Med Chem.* 2010;53:2779-2796.
4. Park K, Tomlins SA, Mudaliar KM, et al. Antibody-based detection of ERG rearrangement-positive prostate cancer. *Neoplasia.* 2010;12:590-598.
5. Ezhkova E, Pasolli HA, Parker JS, et al. Ezh2 orchestrates gene expression for the stepwise differentiation of tissue-specific stem cells. *Cell.* 2009;136:1122-1135.

Castrate-Resistant Prostate Cancer—New Therapeutic Approaches

At the AUA meeting, Dr. Martin Gleave discussed new therapeutic approaches to CRPC.[1] The treatment of CRPC has been revolutionized with the introduction of several major agents in recent months. A paradigm-changing newcomer to the treatment of mCRPC is the immunotherapy sipuleucel-T. Sipuleucel-T was established as an effective therapy for men with asymptomatic or minimally symptomatic mCRPC in the IMPACT trial, a phase III clinical trial by Kantoff and colleagues.[2] The final analysis of this trial showed a significant OS benefit attributed to sipuleucel-T compared with placebo, which was demonstrated by a 22% relative reduction in the risk of death (HR; 0.78; 95% CI, 0.61–0.98; *P*=.03). This reduction translated to a 4.1-month improvement in median OS (25.8 vs 21.7 months), and an increase in the 3-year OS rates (32.1% vs 23.0%). However, despite this significant improvement in patient survival, many unresolved issues remain regarding the use of this immunotherapy to treat mCRPC. For example, it is known that relatively few (2%) patients achieve a PSA response with sipuleucel-T, and clinical changes also tend not to occur with this treatment. Therefore, it is difficult to judge response to therapy, and little is known about how to adequately predict which patients will benefit from treatment. Further, the optimal timing of sipuleucel-T has not yet been established, especially regarding its proximity to steroid use and whether it should be administered prior to or following secondary hormonal therapy. Current studies are now addressing these important questions.

Based on the success of sipuleucel-T in CRPC, other immunotherapies are also under investigation in men with prostate cancer. For example, PROSTVAC is being prospectively evaluated in men with asymptomatic or minimally symptomatic mCRPC, while ipilimumab is in a phase III clinical trial for evaluation in both chemotherapy-naïve and previously chemotherapy-treated men with CRPC.

Another important drug that has recently been approved for the prevention of skeletal-related events in patients with bone metastases from solid tumors is denosumab. This monoclonal antibody is directed against the RANK ligand (RANKL), and through binding to RANKL, it inhibits osteoclast formation, function, and survival, thus preventing bone resorption. Compared with zoledronic acid, denosumab prolonged the median time to first skeletal-related event by 18% in men with prostate cancer (20.7 vs 17.1 months, HR, 0.82; 95% CI, 0.71–0.95; *P*=.008).[3] A separate phase III study which compared denosumab with placebo in CRPC showed that denosumab was associated with a sig-

ABSTRACT SUMMARY An Evaluation of Clusterin Antisense Inhibitor OGX-011 in Combination With the Second-Generation Antiandrogen MDV3100 in a Castrate-Resistant Prostate Cancer Model

The antisense oligonucleotide OGX-011 targets clusterin and has been shown to possess anticancer activity in both preclinical and clinical studies. In this study by Matsumoto and colleagues (ASCO Abstract 4502), the combination of MDV-3100 with OGX-011 synergistically delayed LNCaP prostate cancer cell growth and also increased apoptosis, evidenced by both an increase in the sub-G0/G1 fraction of cells following treatment, as well as the amount of poly(ADP-ribose) polymerase (PARP) cleavage present. In an LNCaP CRPC xenograft, the addition of OGX-011 and MDV3100 synergistically delayed castrate progression, shown by both greater tumor growth inhibition as well as delayed time to PSA progression. Three potential molecular mechanisms were proposed to explain the synergistic activity demonstrated between MDV3100 and OGX-011, including 1) decreased androgen receptor stability via suppression of heat shock factor protein (HSF)-1 (HSF-1)-mediated regulation of androgen receptor co-chaperone proteins (including FKBP52 and Hsp27); 2) OGX-011-mediated decrease of MDV3100-induced Akt signaling; and 3) OGX-011-mediated decrease of MDV-3100-induced autophagy. Although MDV3100 treatment alone did not affect androgen receptor protein expression, the combination with OGX-011 resulted in marked decreased protein expression. This decrease was not due to a change in mRNA level, but instead to an increase in androgen receptor proteasome degradation. The combination of the 2 agents maximally suppressed expression of androgen receptor-dependent genes, including PSA and TMPRSS2.

ABSTRACT SUMMARY Effect of Abiraterone Acetate On Pain Control And Skeletal-Related Events in Patients With Metastatic Castration-Resistant Prostate Cancer Post Docetaxel: Results from the COU-AA-301 Phase III Study

Logothetis and colleagues investigated the effect of abiraterone treatment on bone-related symptoms in the COU-AA-301 study (ASCO Abstract 4520). A pre-specified analysis included time to skeletal-related events, proportion of patients with palliation of pain intensity, and time to progression of pain intensity. Exploratory analyses included the proportion of patients with palliation of pain interference, and time to progression of pain interference. A total of 1,195 mCRPC patients (median age: 69 years, range: 39–95) were included; all patients had experienced disease progression following prior docetaxel therapy. Metastasis-related symptoms at baseline were well distributed between the abiraterone and placebo treatment groups, including the frequency of significant pain (44.3% and 44.0%). A similar proportion of patients in each arm had either bone (89.2% and 90.4%) or visceral (29% and 24.1%) metastases. Significantly, treatment with abiraterone plus prednisone resulted in marked improvements in all measures of bone pain symptom control versus placebo plus prednisone, including palliation of pain intensity (44.4% vs 27.0%; *P*=.0002) and palliation of pain interference (59.2% vs 38.0%; *P*=.0004). The median time to palliation of pain intensity (5.55 vs 10.25 months; *P*=.001) and pain interference (1.02 vs 3.71 months; *P*=.0009) was significantly shortened in the abiraterone treatment group. Further, patients in the abiraterone arm had a significant delay in the time to first skeletal-related event compared with patients in the placebo arm (301 vs 150 days; *P*<.0001). According to a measure of the mean worst pain score, immediate and sustained improvements were observed in bone-related symptoms with abiraterone plus prednisone, compared with prednisone alone. Pain control was improved by day 15 of cycle 1, and this benefit was sustained through cycle 10.

nificant improvement in median bone metastasis-free survival (HR: 0.85, 95% CI, 0.73-0.98; *P*=.03). That study also demonstrated that denosumab significantly improved time to first occurrence of bone metastases.

Prior to the recent approval of targeted therapies, docetaxel in combination with prednisone was the only agent approved for the treatment of mCRPC. In an effort to improve upon the relatively low efficacy achieved with the currently used docetaxel regimen, several studies are testing novel docetaxel-based combinations and comparing them to standard therapy (docetaxel plus prednisone). Examples of novel combinations include docetaxel with bevacizumab, VEGF-trap, lenalidomide, atrasentan, ZD4054, and dasatinib. One novel combination is with the clusterin inhibitor OGX-011, which was evaluated as first-line therapy in men with CRPC.[4] Notably, the addition of OGX-011 to docetaxel, versus docetaxel alone, significantly prolonged the median OS (23.8 vs 16.89 months; HR, 0.49; 95% CI, 0.29–0.97; *P*=.01). Several variables were identified to be predictive of OS in a multivariate analysis, including performance status (*P*<.0001) and presence of visceral metastasis (*P*=.01).

Other investigative efforts are focused on how best to treat mCRPC patients in the post-docetaxel setting. Recently, cabazitaxel and abiraterone were approved for this indication, providing these patients with important treatment alternatives.

Targeting the androgen receptor remains an important strategy in the treatment of CRPC, with emphasis on decreasing the amount of ligand available for binding to the receptor (eg, with abiraterone and TAK-700), decreasing overall androgen receptor levels (eg, with chaperone inhibitors), and blocking ligand binding to the androgen receptor (eg, with MDV3100). Based on promising activity demonstrated in an initial study, MDV3100 is now under evaluation in 2 phase III registration trials.

Thus, it is becoming increasingly apparent that understanding mechanisms of CRPC will yield promising new targets in the treatment of CRPC. This rationale for drug development, guided by an understanding of the tumor biology and coupled with intelligent clinical trial design, will hopefully lead to many new advancements, combinations, and new agents for the treatment of this disease.

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Circulating Tumor Cells

At the 2011 American Society of Clinical Oncology (ASCO) meeting, Dr. Nancy Dawson discussed the role of circulating tumor cells (CTCs) as a biomarker for prostate cancer.[1] Until now, PSA has been the only biomarker integrated into routine clinical practice. However, the usefulness of PSA in guiding treatment and, most importantly, impacting outcomes, may be limited. As Dr. Dawson described, measuring and monitoring CTCs could help inform clinical decision-making and benefit patients.

CTCs are tumor cells that leave the primary tumor, enter a blood vessel, and metastasize. These cells can be detected via several methods, with the CellSearch Assay being the only approach approved by the US Food and Drug Administration (FDA). This assay uses immunomagnetic labeling and immunofluorescent identification to find cells that are positive for CK8, CK18, or CK19, that have an intracellular nucleus, are negative for CD45, and are at least 4 µ-mm in size.

Measuring CTCs has so far not shown clinical usefulness for localized prostate cancer. Although many patients harbor CTCs, they are not correlated with tumor volume, pathologic stage, or Gleason score. This biomarker has shown relevance for metastatic, hormone-sensitive prostate cancer. An ongoing study by the Southwest Oncology Group of hormonal therapy plus an investigational drug for metastatic disease will examine the correlation between CTCs and outcome, which should help clarify this relationship.

The most impressive data on CTCs is in the setting of mCRPC. In a 231-patient study of mCRPC, CTCs were measured at baseline, at 2–5 weeks, 6–8 weeks, 9–12 weeks, and 13–20 weeks during the course of therapy. Patients were classified as having a favorable or unfavorable CTC count at each interval. Patients with a baseline CTC count of less than 5 experienced a median OS of 21.7 months, versus 11.5 months for patients with a baseline count of 5 or greater. Interestingly, Goodman and colleagues have found a significant survival difference between patients with a baseline CTC count of 4 or greater and those with a CTC count of less than 4.[2]

Although the role of CTC count as a prognostic indicator of outcome has been clarified, whether or not its measurement can alter outcomes is more pertinent to patient care. In addressing this issue, Dr. Dawson referred again to the data showing

ABSTRACT SUMMARY Safety, Efficacy, and Pharmacodynamics of the Investigational Agent TAK-700 in Metastatic Castration-Resistant Prostate Cancer: Updated Data from a Phase I/II Study

TAK-700 is a selective and reversible nonsteroidal inhibitor of the 17,20-lyase enzyme. By inhibiting this enzyme, TAK-700 can interfere with the production of androgens that are synthesized in the testes and adrenal glands. Agus and colleagues conducted an open-label, dose-escalation, phase I/II trial, with the aim of evaluating the safety and tolerability of different TAK-700 doses in patients with mCRPC (ASCO Abstract 4531). During the phase I portion of this trial, TAK-700 was shown to have a manageable safety profile and to effectively suppress the production of testosterone, DHEA, and PSA. TAK-700 was administered daily in 28-day cycles for at least 6 months. A total of 4 nonrandomized dose cohorts were used, including 300 mg twice daily, 400 mg twice daily (plus 5 mg prednisone twice daily), 600 mg twice daily (plus 5 mg prednisone twice daily), and 600 mg once daily. The median PSA at diagnosis was 22 ng/mL (range: 1.9–999.0), and patients were primarily (86%) white. A number of patients (40%) had unknown disease stage; the rest of the population had stage I (8%), stage II (14%), stage III (20%), and stage IV (16%) disease. At the time of study analysis, 39 patients remained on therapy. Approximately half (53%) achieved a PSA decrease of 50% or greater at 12 weeks (45% in the intent-to-treat population), while 64% achieved a PSA decrease of 50% or greater at 24 weeks (38% in the intent-to-treat population). Interestingly, most patients classified as nonresponders had received prior therapy with ketoconazole. Partial responses were reported in 12% of patients (25% in the 300 mg TAK-700 group, 20% in the 400 mg TAK-700 plus prednisone group, 6% in the 600 mg TAK-700 plus prednisone group, 0% in the 600 mg TAK-700 once daily group). The most frequently reported grade 3 or higher treatment-related adverse events were fatigue, nausea, constipation, diarrhea, headache, and anorexia. One-quarter of patients (26%) had serious adverse events.

ABSTRACT SUMMARY Quality of Life Assessment in a Randomized, Double-Blind Study of Sipuleucel-T in Men With Androgen Dependent Prostate Cancer

Sipuleucel-T was recently evaluated in the double-blind, controlled study P-11, in which 176 men with androgen-dependent prostate cancer were enrolled, received ADT, and were then randomized to treatment with either sipuleucel-T or control. Here, Beer and colleagues conducted a quality of life assessment of patients in the P-11 trial (ASCO Abstract 4648). Quality of life was assessed using 3 instruments: the Fatigue Inventory (0-10 scale which included assessment of the worst fatigue level over the past 24 hours); the Linear Analogue Self-Assessment Scale (0-100 scale), and the Global Rating of Change (same vs worse vs better, relative to baseline, 13 weeks prior to baseline, and week 13 and week 26). Almost all patients (98%) enrolled in the P-11 trial completed a quality of life assessment at baseline, and most (92%) had at least 1 post-treatment quality of life assessment. During the ADT period, prior to randomization, measures of quality of life declined; however, these results were consistent with what is known about the effects of androgen deprivation therapy. No significant differences were reported between sipuleucel-T and control for any of the quality of life assessments used, at either week 13 or week 26. In addition, most patients (>90%) in both treatment groups (sipuleucel-T and control) reported "same" or "better" in the Global Rating of Change assessment compared with baseline.

that patients whose CTC count converts from unfavorable to favorable experience outcomes similar to those who began treatment with a favorable CTC count.

In addition, Olmos and associates found that progression-free survival was longer among mCRPC patients who either began with a favorable CTC count or converted from unfavorable to favorable during the course of treatment compared to patients whose CTC count remained unfavorable throughout their treatment.[3] Olmos and associates also compared CTC with PSA as predictors of OS time.[3] They reported a significant difference in OS between patients with a CTC count of less than 5 versus greater than 5 during each measured interval (2–5 weeks, 6–8 weeks, 9–12 weeks, and 13–20 weeks). The difference in OS between patients with a favorable versus unfavorable CTC count was significant at all measured intervals (P<.0001 throughout). By contrast, a 30% decline in PSA was not associated with an improved OS at 2–5 weeks. This biomarker was predictive of a survival advantage beginning at 6–8 weeks and at each subsequent interval. According to a more recent report in the *New England Journal of Medicine* by De Bono and colleagues of 1,200 mCRPC patients randomized to receive abiraterone versus placebo plus prednisone, CTCs were shown to be a surrogate for survival among these patients.[4]

An ongoing breast cancer trial may indicate how CTC count will be used in mCRPC treatment in the future. In this study, patients who begin treatment with a favorable CTC count or who convert from unfavorable to favorable continue on their first-line chemotherapy, whereas those who have an unfavorable count that persists are randomized to remain on first-line therapy or switch to an alternate regimen. Survival and progression times will be compared for all patients, revealing whether CTC counts can be used to determine the course of therapy. A similar approach in an mCRPC trial would help clarify the role of this biomarker in prostate cancer treatment.

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Prostate-Specific Antigen Kinetics

At the ASCO meeting, Dr. Mark Garzotto discussed the evolving relevance of PSA in the care of patients with prostate cancer.[1] As he noted, prostate cancer is an extremely heterogeneous disease, which makes stratifying patients to appropriate therapies challenging. Biomarkers could help reduce this confusion by clarifying which therapy is most appropriate for which patients.

PSA kinetics, which include doubling time and velocity (and, less commonly, slope), may provide a real-time measurement of the change in tumor burden over time, giving a useful insight into a patient's response to treatment. Numerous studies have evaluated the potential role of PSA kinetics as an indicator of outcomes, with varying conclusions. Dr. Garzotto highlighted several key publications pointing to the role of PSA as an important aid in treatment considerations and in helping patients weigh options.

The Baltimore Longitudinal Study, which began PSA measurements at 10 years prior to diagnoses, provides useful insights into the role of PSA as a biomarker.[2] Individuals enrolled in the study who developed either benign prostatic hyperplasia or locoregional disease tended to have low PSA levels prior to diagnosis, whereas those who developed metastatic disease already had comparably high PSA levels at that same time interval. Interestingly, when the PSA measurement was less than 10, PSA doubling time and PSA velocity were of limited clinical utility, perhaps due to competing factors such as inflammation and PSA leaks.

Dr. Garzotto reviewed several other findings. A study by his group found that a PSA doubling time of greater than 5 years was associated with a reduced risk of prostate cancer. Klop and colleagues stratified patients according to PSA doubling time and found that a shorter doubling time was associated with a hazard ratio of more than 8.5 for recurrence following prostatectomy or radiation. However, an active surveillance study at Johns Hopkins University found no significance of PSA doubling time or PSA velocity as risk factors following prostatectomy.

Evaluating the role of PSA in primary therapy, where patients have undergone prostatectomy, can give a particularly useful insight into the utility of this biomarker. Takamiya and colleagues found that PSA slope was predictive of prostate cancer–specific mortality,[3] and other data show that PSA doubling time was highly predictive of metastases among patients who recurred following primary therapy.

A study by Pound and colleagues of patients who had undergone surgery found that a PSA doubling time

ABSTRACT SUMMARY Time to Disease-Related Pain After Sipuleucel-T in Asymptomatic Patients With Metastatic Castrate Resistant Prostate Cancer: Results From Three Randomized Phase 3 Trials

Small and colleagues reported on an analysis of prospectively collected time to disease-related pain data from 428 patients from 3 phase III trials: IMPACT, D9901, and D9902A (ASCO Abstract 4661). Time to disease-related pain status was collected at either time of disease-related pain or for 4 weeks following disease progression, whichever occurred first. Although time to disease-related pain was originally a co-primary endpoint of the IMPACT study, the protocol was later amended to allow minimally symptomatic patients, and therefore it was removed as an endpoint. In studies D9901 and D9902A, time to disease-related pain was a secondary endpoint. The median time to disease-related pain in each study was not significant in any of the 3 studies. The integrated analysis was also not significantly different (HR: 0.844, 95% CI, 0.635–1.122; *P*=0.241) In the integrated analysis, the data showed a trend towards delayed median time to disease-related pain in the sipuleucel-T group compared with control (5.6 vs 5.3 months). The 12-month pain-free estimates were prolonged in the sipuleucel-T group (39.3 vs 18.9 months). An analysis of the baseline predictors revealed several which independently predicted time to disease-related pain, including higher PSA (HR: 1.264, 95% CI, 1.133–1.409; *P*<.001), higher alkaline phosphatase (HR: 1.486, 95% CI, 1.208–1.828; *P*<.001), lower age (HR: 0.977, 95% CI, 0.961–0.993; *P*=.005), bisphosphonate use (HR: 1.600, 95% CI, 1.171–2.188, *P*=.003), and prior radiation therapy (HR: 1.596, 95% CI, 1.199–2.126; *P*=.001). Multivariate analysis showed the trend towards a sipuleucel-T treatment effect became stronger after adjusting for significant independent predictors (HR: 0.80, 95% CI, 0.60–1.08; *P*=.14).

ABSTRACT SUMMARY Evaluation of Circulating Tumor Cell Enumeration as an Efficacy Response Biomarker of Overall Survival in Metastatic Castration-Resistant Prostate Cancer

Scher and colleagues presented results from a preplanned analysis of the COU-AA-301 trial, which investigated the potential of using CTC enumeration as a viable surrogate biomarker for predicting OS following abiraterone treatment (ASCO Abstract LBA4517). The 1,195 patients enrolled in the trial were randomized in a 2:1 fashion to receive either abiraterone plus prednisone or placebo plus prednisone. Patient CTCs were collected via immunomagnetic selection, which was followed by a digital image analysis. CTCs were defined as positive if they were intact, DAPI- and EpCAM-positive, and CD45-negative. The number of CTCs identified was reported per 7.5 mL of blood; a favorable CTC count was considered to be less than 5 CTC per 7.5 mL blood, while an unfavorable CTC count was considered to be at least 5 CTC per 7.5 mL blood. This second preplanned analysis, which occurred prior to crossover from placebo to abiraterone, accounted for a total of 775 events. At this analysis, the absolute median OS benefit associated with abiraterone was 4.6 months (15.8 vs 11.2 months for abiraterone vs placebo, respectively, HR: 0.74, 95% CI, 0.638–0.859; *P*<.0001). The CTC enumeration data were shown to be highly concordant between screening and baseline values, suggesting little variance between these 2 time points. Improved median OS was associated with abiraterone versus placebo in patients with both favorable (22.1 vs 19.7 months) and unfavorable (10.9 vs 8.2 months) CTC counts at baseline. Importantly, the rates of CTC conversion (from unfavorable to favorable) were significantly higher among abiraterone-treated patients versus placebo-treated patients, at week 4 (42% vs 14%; *P*<.0001), week 8 (50% vs 17%; *P*<.0001), and week 12 (48% vs 17%; *P*<.0001). CTC count at baseline was significantly prognostic for survival in a multivariate analysis (HR: 1.19, 95% CI, 1.137–1.245; *P*<.0001).

of less than 10 months was associated with the development of metastases.[4] Here, prostate cancer–specific mortality was 25-fold higher among patients with the shortest PSA doubling time (less than 3 months) compared to those with a doubling time of greater than 15 months. OS was also much shorter among the former group. In an update to this study, Pound and associates reported findings based on 423 patients with an 8-year follow-up. The PSA doubling time was predictive of metastatic presentation: among those with a doubling time of less than 3 months, approximately half of patients had metastatic disease by 1 year following primary therapy. By contrast, half of those with a doubling time of 3–9 months had metastatic disease at 4 years.

For patients with mCRPC, Nelson and coworkers found that PSA velocity was associated with a risk of metastases among 474 patients enrolled in the control arm of an adjuvant treatment study.[5] PSA velocity accurately predicted time to metastasis and time of bone metastasis, though the data did not correlate with overall survival. Similarly, a study by Smith and colleagues of zoledronic acid versus placebo for non-metastatic, castrate-resistant prostate cancer found that PSA measures were strongly associated with time to metastasis, OS, and bone metastases–free survival.[6]

Dr. Garzotto noted several other studies that showed PSA kinetics to be useful in the metastatic setting, with both PSA velocity and PSA doubling time associated with decreased overall survival and increased mortality due to prostate cancer. Many other markers of prostate cancer progression, such as age, pain, anemia, and elevated alkaline phosphatase were also associated with decreased overall survival and increased mortality.

Importantly, Dr. Garzotto noted that although PSA kinetics are not yet applicable for guiding therapeutic decisions, these measurements can be used as an aid in consultations. PSA data can be considered when discussing prostate cancer–specific mortality, risk of metastases, potential survival time, and whether patients should consider enrollment in a clinical trial. Therefore, it is essential that PSA kinetics be incorporated into clinical trials so that their relevance can continue to be studied.

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Commentary

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Until recently, no new drugs had received approval from the US Food and Drug Administration (FDA) for patients with metastatic castration-resistant prostate cancer (mCRPC). However, starting in 2010, 3 new drugs have gained regulatory clearance after being proven to prolong survival. Most impressively, these agents all have unique mechanisms of action. Cabazitaxel is a novel taxane that offered a survival benefit over mitoxantrone in a randomized, phase III trial of 755 men whose disease had progressed during or after docetaxel chemotherapy.[1] Abiraterone, a potent CYP 17,20 lyase inhibitor, was just approved by the FDA in April 2011 for men with mCRPC who have received prior docetaxel chemotherapy.[2] At an interim analysis of the COU-AA-301 trial, overall survival was longer in the abiraterone with prednisone group than the placebo with prednisone group (median 14.8 vs 10.9 months; HR, 0.65; 95% CI, 0.54–0.77; P<.001). Finally, in a 2:1 randomized, phase III trial of 512 men with asymptomatic or minimally symptomatic mCRPC, sipuleucel-T—an autologous active cellular immunotherapy—offered a 22% reduction in the risk of death over placebo (HR, 0.78; 95% CI, 0.61–0.98; P=.03).[3] This resulted in a median survival improvement of 4 months, from 21.7 months in the placebo group to 25.8 months in the sipuleucel-T group. With these new drugs on the market, we are now faced with the challenge of learning how best to use them to maximum benefit for our patients with mCRPC.

The story with abiraterone is not a completely new one; however, the unique property of abiraterone is that it can inhibit production of intratumoral androgens. Multiple groups have shown that androgen levels within prostate tumors can be maintained at high levels, even when patients are castrate by serum testosterone standards.[4,5] Transcripts of enzymes generally present in the adrenal gland that lead to synthesis of androgens are also expressed at high levels within the tumor.[5] A phase I study of abiraterone was able to show significant suppression of serum androgens with supersensitive assays that utilized liquid chromatography

ABSTRACT SUMMARY Post-Progression Treatment With APC8015F May Have Prolonged Survival of Subjects in the Control Arm of Sipuleucel-T Phase 3 Studies

APC8015F is an autologous immunotherapy made from cryopreserved peripheral blood mononuclear cells. Gomella and colleagues presented an analysis of a phase II, open-label trial of APC8015F for patients who had participated in 1 of 3 phase III studies examining sipuleucel-T (ASCO Abstract 4534). Three phase III trials have demonstrated a survival prolongation among patients who received sipuleucel-T versus placebo. According to the report by Gomella and colleagues, APC8015F may have contributed to that survival advantage. All patients had received sipuleucel-T or a control treatment every 2 weeks for 3 weeks. Upon progression, patients could be enrolled into this phase II, open-label protocol, which measured overall survival as its primary endpoint. A total of 155 patients received 3 separate infusions of APC8015F, and 61 patients were enrolled in a control arm. Overall survival following disease progression was measured for patients who had undergone treatment with sipuleucel-T and APC8015F, patients who had undergone treatment with APC8015F alone, and a control group who had received the placebo in the sipuleucel-T trial and were then enrolled to the control arm in the present study. The study found evidence of clinical activity for APC8015F. Control patients given APC8015F had improved post-progression OS compared to untreated control patients (20.0 months versus 9.8 months, respectively). Control patients who received APC8015F experienced more of the most common adverse events compared to those who did not receive APC8015F, but fewer adverse events than patients treated with sipuleucel-T.

EDUCATION SESSION Management of Castration-Resistant Prostate Cancer

At the AUA meeting, Dr. Fred Saad discussed the treatment options for men with CRPC. CRPC patients who are relatively asymptomatic are generally initially treated with secondary hormonal treatments, with the understanding that the androgen receptor pathway likely remains active in most patients who develop castration-resistant disease. Sipuleucel-T is associated with a significantly improved OS compared with placebo. Systemic chemotherapy is another treatment option for men with CRPC, although only for those with detectable macroscopic metastatic disease. Based on results from 2 large, randomized, controlled trials, docetaxel plus prednisone is considered a standard of care for this stage of disease, providing superior OS benefit compared to the previous standard of mitoxantrone plus prednisone. Docetaxel-based chemotherapy is still the only strategy that has demonstrated an OS benefit in most men with mCRPC, independent of whether or not they are symptomatic or have visceral metastases. New agents targeting the androgen axis have also been recently developed, renewing the enthusiasm once held for manipulating the hormone pathway in prostate cancer. For the post-docetaxel setting, abiraterone plus prednisone is now approved, based on a significant improvement in OS compared with placebo plus prednisone. Until recently, mitoxantrone was considered the treatment of choice for second-line chemotherapy. However, the systemic agent cabazitaxel is now the standard of care for this setting, based on improved survival rates. In men with CRPC and bone metastases, zoledronic acid or denosumab is indicated to prevent disease-related skeletal complication.

tandem mass spectrometry.[6] It was not surprising to ultimately see this translate into a survival benefit, even in a very advanced chemotherapy pretreated mCRPC population, reminding us that the terms "androgen-independent" and "hormone-refractory" are significant misnomers.

At the ASCO annual meeting in 2011, we learned more about the clinical benefits of abiraterone. Logothetis and associates performed a prespecified analysis of pain intensity from the COU-AA-301 trial and found improvement in the abiraterone group compared to the placebo group (44.4 vs 27%; *P*=.0002).[7] They also found improvement in time to pain progression (25th percentile 7.39 vs 4.67 months; *P*=.0056). Time to skeletal-related event was 301 versus 150 days (*P*=.006). Early results from an ongoing phase II trial of ketoconazole-pretreated, chemotherapy-naïve men with mCRPC confirmed biologic activity of abiraterone post-ketoconazole.[8] Confirmed 50% or greater and 30% or greater decline in prostate-specific antigen (PSA) at 12 weeks occurred in 3 of 14 (21%) and 6 of 14 (43%) patients, respectively. Although a number of patients with prior ketoconazole exposure respond to abiraterone, these response rates are lower than what was reported in the phase I study of this patient population, in which 9 of 19 (47%) with prior ketoconazole compared with 9 of 14 (64%) without prior ketoconazole had a 50% or greater PSA decline to abiraterone treatment.[9] A most interesting ASCO 2011 presentation was an exploratory analysis showing that those patients without detectable DHEA prior to starting abiraterone did not respond to therapy. The ultimate goal will be to discover a predictive biomarker for future abiraterone treatment response, and further confirmation of these findings with larger patient numbers and a commercially available assay will be necessary.

In addition to abiraterone, other androgen synthesis inhibitors are being developed and were presented at ASCO. TAK-700 is a selective 17,20 lyase inhibitor; updated phase I/II results from the study of TAK-700 were presented by Dreicer on behalf of his colleagues at the meeting.[10] Regardless of dosing levels and schedules or the presence or absence of prednisone, 50% or greater PSA decreases at 12 weeks occurred in 44 of 83 (53%), with 90% or greater reductions in 21 of 83 (25%), and Response Evaluation Criteria in Solid Tumor (RECIST) partial responses in 6 of 49 (13%) patients. Multiple other studies with TAK-700 are ongoing, and a randomized, control trial of 400 mg of TAK-700 twice daily or placebo, with prednisone 5 mg twice daily, was highlighted at the meeting.[11] Primary outcomes for this actively enrolling phase III trial are overall survival and radiographic progression-free survival with planned enrollment of 1,454 patients.

Another approach to inhibiting the androgen-androgen receptor (AR) axis is to directly bind the AR to inhibit ligand binding of androgens. MDV3100 is an AR antagonist that lacks the partial agonist activity seen with bicalutamide, preventing nuclear translocation and co-activator recruitment of the ligand-receptor complex.[12] A phase I/II trial of MDV3100 in 140 men with CRPC showed significant activity at all doses; however, 3 (2%) men had seizures at doses at or above 360 mg/day.[13] As a result, a dose of 160 mg/day was used

in a now fully accrued, randomized, phase III, placebo-controlled trial for patients with mCRPC who have received previous docetaxel chemotherapy. Another randomized, phase III, placebo-controlled trial for patients with mCRPC who have not received previous docetaxel is actively accruing patients.

At ASCO 2011, we gained more insight into the biology of MDV3100. Increased pretreatment concentration of CYP17 (P=.002) and testosterone (P=.019) from bone marrow aspirates from 44 patients with bone mCRPC predicted for those who would have a 50% or greater or less than 50% PSA decline.[14] From a smaller subset of those 44 patients, reduced nuclear AR expression in the bone marrow after 8 weeks of treatment with MDV3100 also corresponded with 50% or greater PSA decline. Not surprisingly, both plasma (P<.0001) and bone marrow (P<.001) testosterone and plasma dihydrotestosterone (P=.008) assessed by electrospray tandem mass spectrometry consistently increased in response to treatment with MDV3100. Although these biologic results are fascinating, it is not clear what proportion of bone marrow–aspirated cells constituted actual tumor cells, which certainly could impact the results.

With many new active hormonal agents for men with CRPC, exploring novel combinations has become interesting. OGX-011 (custirsen) is an antisense to clusterin, an anti-apoptotic protein, that revealed a survival benefit in a randomized phase II trial for men with mCRPC receiving docetaxel plus prednisone plus OGX-011 640 mg IV weekly when compared to docetaxel plus prednisone.[15] At ASCO 2011, a preclinical study with an AR-positive LNCaP cell line showed OGX-011 to be synergistic with MDV3100 in a dose- and time-dependent manner compared to monotherapy with either agent alone.[16] OGX-011 accelerated AR degradation and repressed AR transcriptional activity in combination with MDV3100. Combination therapy also delayed time to tumor and PSA progression over scramble oligonucleotide with MDV3100 in a xenograft model. This study provides preclinical data for combination therapy to be brought to the clinic to potentiate AR targeting in humans.

With multiple agents in development targeting the androgen-AR axis, the field is left with the challenge of understanding drug resistance mechanisms, proper sequencing of agents, rational combinations, and potential introduction of agents at earlier disease states. Although CYP17A polymorphisms exist and may represent patients who have better long-term outcomes,[17] further investigation will be required to establish definite ties to response to new agents like abiraterone. In animal models, resistance to abiraterone is accompanied by upregulation in CYP17A, full length AR, and spliced-variant AR.[18] As new agents, like abiraterone, are introduced in earlier disease states, efficacy will become more challenging to prove, and toxicity concerns will become more prominent. For example, abiraterone is currently administered with prednisone to prevent excess mineralocorticoid production. The long-term toxicities of steroids will need to be balanced with clinical benefit from abiraterone. With further investigation, it may eventually be possible to select patients who can use abiraterone without or with lower doses of steroids.

Sipuleucel-T is the first FDA-approved immunotherapy for a

EDUCATION SESSION Immunotherapy in Castration-Resistant Prostate Cancer

At the ASCO meeting, Dr. Charles Drake reviewed ways to integrate sipuleucel-T into patient care, including how to manage and monitor patients following therapy. Administration of sipuleucel-T involves a complex process of harvesting the patient's white blood cells. The cells are incubated with the target antigen (prostatic acid phosphatase) and GM-CSF, and are then infused back into the patient. This process is repeated every 2 weeks for a total of 3 infusions. The IMPACT study randomized patients with mCRPC with no visceral metastases to undergo treatment with sipuleucel-T (n=341) or placebo (n=171). The median OS was 25.8 months versus 21.7 months, respectively (P<.032). The precise mechanism of action of sipuleucel-T is still under investigation, but antibody data appear consistent with an adaptive immune response. The viral vaccine Prostvac has also been studied in a recent small clinical trial. The experimental agent (n=82) was associated with a median time to progression—the primary endpoint—of 25.1 months, versus 16.6 months for the control arm (n=40). Prostvac plus low-dose adjuvant GM-CSF is now being tested in a large, global phase III clinical trial. CTLA4 uses cellular signals that normally activate T cells to inactivate them instead. The monoclonal antibodies ipilimumab and tremelimumab block that immune checkpoint. A randomized, double-blind phase III trial of ipilimumab versus placebo following radiation therapy among patients with CRPC who have failed docetaxel therapy is currently in progress. Today's treatment algorithm integrates sipuleucel-T after androgen ablation therapy for many mCRPC patients, prior to docetaxel therapy. Prostvac and ipilimumab will likely find a place in the treatment of CRPC as trial results become available.

ABSTRACT SUMMARY Genomic Analysis of Circulating Tumor Cells From Patients With Castration-Resistant Prostate Cancer as Predictive Biomarkers

Danila and associates utilized the prostate genomic profiling project at Memorial Sloan-Kettering Cancer Center in order to investigate the frequency of gene mutations identified in CTC from patients with CRPC (ASCO Abstract 4540). A total of 124 patients with progressive CRPC had their blood sampled and processed by fluorescence-activated cell sorting (FACS) methodology, which enriched EpCAM+, CD45-, and DAPI- cells. The processed samples isolated an average of 100 times more EpCAM+ events compared to the CellSearch System. The FACS technique isolated more than 10 or more than 50 events in 88% and 58% of patients, respectively; 32% and 10% of these patients were shown to have unfavorable CTC counts (>5 cells/7.5 mL) when using CellSearch, respectively. Prostate-specific mRNAs (PSA, AR, TMPRSS2-ERG) were expressed by the isolated EpCAM+ events, and as few as 50 EpCAM+ events yielded enough high-quality DNA for acceptable genomic sequencing coverage. There was a recovery rate of 89% from FACS-sorted samples. The detection threshold of a mutation was recognized at 1:4 alleles in a heterogeneous cell population. Further assessment is being conducted in select missense mutations in AR and TP53 that were present in CTC but not in paired white blood cells.

solid tumor, and it represents a novel mechanism of action for prostate cancer therapy. Initially, a pooled analysis of 2 small, randomized, controlled trials revealed an overall survival benefit over placebo with minimal toxicity[19]; this trial was followed by the larger randomized, phase III IMPACT trial,[3] which confirmed these results.

All 3 randomized controlled trials of sipuleucel-T were pooled for separate analyses that were presented at ASCO 2011. From all 3 studies, 165 of 249 (66.3%) patients in the control groups received APC8015F, an autologous immunotherapy made from cells cryopreserved at the time of control generation. Compared to those patients who did not receive APC8015F, treated subjects had better survival (HR, 0.52; 95% CI, 0.37–0.73; *P*=.0001), with a median survival of 20.0 months compared to 9.8 months, respectively.[20] Recognizing that an analysis of this sort would certainly select healthier patients to receive APC8015F, the authors used a Cox regression model fit using backward selection, including a few known independent predictors of postprogression survival. Although there was a potential positive treatment effect to APC8015F (HR, 0.78; 95% CI, 0.54–1.11; *P*=.17), the HR crossed 1 and statistical significance was not met. Another pooled analysis looked at time to disease-related pain from these 3 randomized trials.[21] Although there were trends toward improvement in disease-related pain from sipuleucel-T, none of the integrated results met statistical significance after adjusting for independent baseline predictors of earlier time to disease–related pain.

As with most drugs in oncology, we are currently unable to select patient responders and nonresponders in advance of sipuleucel-T treatment. However, clinicians face another challenge after administration of sipuleucel-T, since objective disease response, PSA decline, and improvement in time to progression are generally not appreciable with this agent. This may be due to the fact that patients with more rapidly progressive disease progress by conventional criteria before sipuleucel-T has had time to be efficacious. This theory may be strengthened by the fact that the Kaplan-Meier survival curves do not begin to separate on the IMPACT trial until the 6-month time point. Thus, a better understanding of the mechanism of action, development of predictive and response biomarkers, and testing in earlier disease states with sipuleucel-T may help alleviate these considerations in the future. Recent work has shown higher antibody titer levels against PA2024, the recombinant fusion protein used to make sipuleucel-T, or prostatic acid phosphatase, which may be reasonable biomarkers of successful response to sipuleucel-T treatment.[3] Further work, however, must be done to help select individual patients most likely to respond to this therapy and to further define drug activity beyond a population-based survival benefit.

One approach is to treat patients with earlier stage disease with sipuleucel-T to allow longer time for the therapy to exert immune effects. Another advantage to such an approach is the ability to provide exposure to sipuleucel-T long before any corticosteroids are indicated. One such trial has been performed in patients with biochemical recurrence after radical prostatectomy, and quality of life data were presented at ASCO 2011. Beer and colleagues randomized 176 patients, 2:1, to sipuleucel-T or control following 3-4 months of androgen-deprivation therapy (ADT). As expected with ADT, the Brief Fatigue Inventory showed decrement in both arms; however, no significant quality of life differences were noted between treatment groups that could be attributable to sipuleucel-T.[22] This observation follows with the known favorable side effect profile shown in previous trials with sipuleucel-T. Another trial for patients with biochemically-recur-

rent prostate cancer after local therapy is planned, and the goal will be to evaluate cellular and serologic immune responses, particularly antibody titers for PA2024. This trial will randomize patients 1:1 to receive sipuleucel-T followed by ADT given 2 weeks after the third infusion or ADT followed by sipuleucel-T, administered 3 months after ADT initiation.[23] Although the commercial adoption of sipuleucel-T use in this very early setting would be challenging given the large number of patients and duration of follow-up necessary to show a meaningful benefit, this trial will provide important immune marker data to help guide the optimal sequencing of ADT with sipuleucel-T. Finally, a global randomized phase III trial comparing sipuleucel-T plus ADT versus ADT alone in men with metastatic hormone-sensitive prostate cancer is planned. This trial will randomize 1,684 men in a 1:1 fashion, with a primary endpoint of overall survival.[24]

With all the new FDA-approved therapies for mCRPC, it is clear that we need to optimize utilization of existing agents, understand resistance mechanisms to aid in drug sequencing, explore rational combinations, and further develop biomarkers to select patients for appropriate therapy with available surrogates for meaningful long-term endpoints. PSA remains the traditional biomarker in the field. For biochemically-recurrent disease, PSA doubling time is one of the best prognostic markers for time to metastasis and overall survival.[25] In the nonmetastatic castration-resistant state, PSA doubling time and absolute PSA level are prognostic for time to the development of bone metastasis.[26] For patients with new hormone-sensitive metastatic prostate cancer, absolute PSA value after 7–8 months of combined ADT is prognostic for overall survival.[27] For patients with mCRPC who are receiving docetaxel chemotherapy, both 30% and 50% PSA declines have been found in separate studies to be prognostic for overall survival.[28,29] However, the above PSA evaluations are generally still considered exploratory, and the FDA will not accept them as surrogates for survival to help approve new agents. Finally, PSA kinetics are not predictive biomarkers that can help select patients for appropriate therapy; they are only prognostic.

Circulating tumor cells (CTCs), enumerated by the CellSearch System, are a prognostic marker for overall survival for those patients with mCRPC starting a new line of chemotherapy.[30] Both baseline measurements and change in response to therapy are independent predictors of overall survival. There are ongoing attempts to establish CTCs as a surrogate marker for survival. Scher and colleagues presented new data from the COU-AA-301 study with abiraterone, which confirmed that a CTC conversion from unfavorable (CTC ≥5) to favorable (CTC <5) was greater in the abiraterone group compared to the placebo group (P<.0001 at 4, 8, and 12 weeks post-treatment).[31] In the multivariate model, treatment with abiraterone (HR, 0.70; 95% CI, 0.59–0.83; P<.0001), baseline LDH (HR, 2.98; 95% CI, 2.5–3.6; P<.0001), and CTC count (HR, 1.19; 95% CI, 1.14–1.3; P<.0001) were all prognostic for survival. Many other randomized, phase III trials for patients with mCRPC have

ABSTRACT SUMMARY A Phase III, Randomized Study of the Investigational Agent TAK-700 Plus Prednisone For Patients With Chemotherapy-Naïve Metastatic Castration-Resistant Prostate Cancer

Patients with mCRPC who have not received prior chemotherapy are being enrolled in a randomized, double-blind, placebo-controlled, multicenter study that seeks to determine the efficacy and safety of TAK-700 plus prednisone when compared with a placebo plus prednisone (ASCO Abstract TPS184). Saad and colleagues aim to evaluate TAK-700 at an early stage of mCRPC, where it may be more efficacious and thus delay the need for chemotherapy. OS and radiographic progression-free survival (rPFS) are the primary study endpoints. Secondary endpoints include the PSA response rate at 12 weeks (decrease by ≥50%), changes in the number of CTC, and time to pain progression. Enrollment is planned for 1,454 patients who meet the following criteria: radiographically documented mCRPC; surgical castration or use of an agent for medical castration; baseline testosterone less than 50 ng/dL; and evidence of disease progression (radiographic or with a rising PSA). Patients must not have received adrenal-targeted therapy or chemotherapy within the past 2 years, and must have no cancer pain or mild pain that does not require opioids. The treatment regimen will consist of either 400 mg of TAK-700 twice daily plus 5 mg of prednisone twice daily, or a placebo plus 5 mg of prednisone twice daily. Interim analyses will be conducted after there have been approximately 412 disease progression events for rPFS, and once approximately 600 deaths for OS have occurred. After their disease progresses and until further antitumor therapy is received, patients may continue to receive TAK-700. There will be an analysis of tumor specimens for candidate biomarkers of TAK-700 antitumor activity, including the TMPRSS2:ERG fusion gene.

ABSTRACT SUMMARY Design of an Open-Label Randomized Phase II Trial Examining the Effect of Sequencing of Sipuleucel-T and Androgen Deprivation Therapy (ADT) on Immune Markers in Prostate Cancer Patients With a Rising Prostate Specific Antigen After Primary Therapy

A clinical trial proposed by Antonarakis and associates will combine ADT with sipuleucel-T in order to examine the role of treatment sequence on immune response markers in patients with non-metastatic prostate cancer who experience a rising PSA following primary therapy (ASCO Abstract TPS189). The main objective of the study is to understand which therapy sequence—ADT started before or after sipuleucel-T—leads to a superior augmentation of immune markers. The maintenance of immune markers over time and the safety profile of sipuleucel-T in this patient population are secondary study endpoints. There will be 60 patients randomized in a 1:1 fashion to receive either sipuleucel-T followed by ADT (administered 2 weeks following the 3rd immunotherapy infusion), or ADT followed by sipuleucel-T (administered 3 months after initiation of ADT). Treatment with ADT will continue through the 18th month in both arms. Investigators are hopeful that a comparison of immune marker responses between these treatment groups will reveal the importance of ADT and sipuleucel-T sequencing in non-metastatic prostate cancer patients with a rising PSA after primary therapy.

also included CTC evaluation, thus validation of the CTC results from COU-AA-301 are forthcoming. Additionally, LDH is a known prognostic marker that now may need to be considered in a panel of biomarkers.

The true utility of CTCs in the future may not come from enumeration but rather from genetic analysis of isolated cells. Genomic analysis has led to identification of missense mutations in AR and TP53 in CTCs, leaving hope that genomic profiling of CTCs may serve as a predictive biomarker to select appropriate patients for individualized therapies.[32]

As we enter a new realm of multiple biologic agents with unique mechanisms of action, developing effective biomarkers is one of the greatest challenges the field of prostate cancer faces. Not only could it help select patients for effective therapy, but it may discern optimal response and appropriate duration of therapy. With reliable and reproducible results, we may ultimately be able to develop and approve new drugs based on biomarkers. As outlined by the events at ASCO 2011, wonderful new changes have occurred recently for men with mCRPC, and with continued research, the outlook can only continue to improve.

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PROVENGE® (sipuleucel-T)
Suspension for Intravenous Infusion **Rx Only**

BRIEF SUMMARY – See full Prescribing Information for complete product information

INDICATIONS AND USAGE: PROVENGE® (sipuleucel-T) is an autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.

DOSAGE AND ADMINISTRATION

- **For Autologous Use Only.**
- The recommended course of therapy for PROVENGE is 3 complete doses, given at approximately 2-week intervals.
- Premedicate patients with oral acetaminophen and an antihistamine such as diphenhydramine.
- Before infusion, confirm that the patient's identity matches the patient identifiers on the infusion bag.
- **Do Not Initiate Infusion of Expired Product.**
- Infuse PROVENGE intravenously over a period of approximately 60 minutes. **Do Not Use a Cell Filter.**
- Interrupt or slow infusion as necessary for acute infusion reactions, depending on the severity of the reaction.

(See Dosage and Administration [2] of full Prescribing Information.)

CONTRAINDICATIONS: None.

WARNINGS AND PRECAUTIONS

- **PROVENGE is intended solely for autologous use.**
- **Acute infusion reactions** (reported within 1 day of infusion) included, but were not limited to, fever, chills, respiratory events (dyspnea, hypoxia, and bronchospasm), nausea, vomiting, fatigue, hypertension, and tachycardia. In controlled clinical trials, 71.2% of patients in the PROVENGE group developed an acute infusion reaction.

  In controlled clinical trials, severe (Grade 3) acute infusion reactions were reported in 3.5% of patients in the PROVENGE group. Reactions included chills, fever, fatigue, asthenia, dyspnea, hypoxia, bronchospasm, dizziness, headache, hypertension, muscle ache, nausea, and vomiting. The incidence of severe events was greater following the second infusion (2.1% vs 0.8% following the first infusion), and decreased to 1.3% following the third infusion. Some (1.2%) patients in the PROVENGE group were hospitalized within 1 day of infusion for management of acute infusion reactions. No Grade 4 or 5 acute infusion reactions were reported in patients in the PROVENGE group.

  Closely monitor patients with cardiac or pulmonary conditions. In the event of an acute infusion reaction, the infusion rate may be decreased, or the infusion stopped, depending on the severity of the reaction. Appropriate medical therapy should be administered as needed.

- **Handling Precautions for Control of Infectious Disease.** PROVENGE is **not** routinely tested for transmissible infectious diseases. Therefore, patient leukapheresis material and PROVENGE may carry the risk of transmitting infectious diseases to health care professionals handling the product. Universal precautions should be followed.

- **Concomitant Chemotherapy or Immunosuppressive Therapy.** Use of either chemotherapy or immunosuppressive agents (such as systemic corticosteroids) given concurrently with the leukapheresis procedure or PROVENGE has not been studied. PROVENGE is designed to stimulate the immune system, and concurrent use of immunosuppressive agents may alter the efficacy and/or safety of PROVENGE. Therefore, patients should be carefully evaluated to determine whether it is medically appropriate to reduce or discontinue immunosuppressive agents prior to treatment with PROVENGE.

- **Product Safety Testing.** PROVENGE is released for infusion based on the microbial and sterility results from several tests: microbial contamination determination by Gram stain, endotoxin content, and in-process sterility with a 2-day incubation to determine absence of microbial growth. The final (7-day incubation) sterility test results are not available at the time of infusion. If the sterility results become positive for microbial contamination after PROVENGE has been approved for infusion, Dendreon will notify the treating physician. Dendreon will attempt to identify the microorganism, perform antibiotic sensitivity testing on recovered microorganisms, and communicate the results to the treating physician. Dendreon may request additional information from the physician in order to determine the source of contamination.

(See Warnings and Precautions [5] of full Prescribing Information.)

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety evaluation of PROVENGE is based on 601 prostate cancer patients in the PROVENGE group who underwent at least 1 leukapheresis procedure in four randomized, controlled clinical trials. The control was non-activated autologousperipheral blood mononuclear cells.

The most common adverse events, reported in patients in the PROVENGE group at a rate ≥15%, were chills, fatigue, fever, back pain, nausea, joint ache, and headache. Severe (Grade 3) and life-threatening (Grade 4) adverse events were reported in 23.6% and 4.0% of patients in the PROVENGE group compared with 25.1% and 3.3% of patients in the control group. Fatal (Grade 5) adverse events were reported in 3.3% of patients in the PROVENGE group compared with 3.6% of patients in the control group.

Serious adverse events were reported in 24.0% of patients in the PROVENGE group and 25.1% of patients in the control group. Serious adverse events in the PROVENGE group included acute infusion reactions *(see Warnings and Precautions)*, cerebrovascular events, and single case reports of eosinophilia, rhabdomyolysis, myasthenia gravis, myositis, and tumor flare.

PROVENGE was discontinued in 1.5% of patients in Study 1 (PROVENGE group n=341; Control group n=171) due to adverse events. Some patients who required central venous catheters for treatment with PROVENGE developed infections, including sepsis. A small number of these patients discontinued treatment as a result. Monitoring for infectious sequelae in patients with central venous catheters is recommended.

Each dose of PROVENGE requires a standard leukapheresis procedure approximately 3 days prior to the infusion. Adverse events that were reported ≤1 day following a leukapheresis procedure in ≥5% of patients in controlled clinical trials included citrate toxicity (14.2%), oral paresthesia (12.6%), paresthesia (11.4%), and fatigue (8.3%).

Table 1 provides the frequency and severity of adverse events reported in ≥5% of patients in the PROVENGE group of randomized, controlled trials of men with prostate cancer. The population included 485 patients with metastatic castrate resistant prostate cancer and 116 patients with non-metastatic androgen dependent prostate cancer who were scheduled to receive 3 infusions of PROVENGE at approximately 2-week intervals. The population was age 40 to 91 years (median 70 years), and 90.6% of patients were Caucasian.

Table 1 Incidence of Adverse Events Occurring in ≥5% of Patients Randomized to PROVENGE

	PROVENGE (N = 601)		Control* (N = 303)	
	All Grades n (%)	Grade 3-5 n (%)	All Grades n (%)	Grade 3-5 n (%)
Any Adverse Event	**591 (98.3)**	**186 (30.9)**	**291 (96.0)**	**97 (32.0)**
Chills	319 (53.1)	13 (2.2)	33 (10.9)	0 (0.0)
Fatigue	247 (41.1)	6 (1.0)	105 (34.7)	4 (1.3)
Fever	188 (31.3)	6 (1.0)	29 (9.6)	3 (1.0)
Back pain	178 (29.6)	18 (3.0)	87 (28.7)	9 (3.0)
Nausea	129 (21.5)	3 (0.5)	45 (14.9)	0 (0.0)
Joint ache	118 (19.6)	11 (1.8)	62 (20.5)	5 (1.7)
Headache	109 (18.1)	4 (0.7)	20 (6.6)	0 (0.0)
Citrate toxicity	89 (14.8)	0 (0.0)	43 (14.2)	0 (0.0)
Paresthesia	85 (14.1)	1 (0.2)	43 (14.2)	0 (0.0)
Vomiting	80 (13.3)	2 (0.3)	23 (7.6)	0 (0.0)
Anemia	75 (12.5)	11 (1.8)	34 (11.2)	7 (2.3)
Constipation	74 (12.3)	1 (0.2)	40 (13.2)	3 (1.0)
Pain	74 (12.3)	7 (1.2)	20 (6.6)	3 (1.0)
Paresthesia oral	74 (12.3)	0 (0.0)	43 (14.2)	0 (0.0)
Pain in extremity	73 (12.1)	5 (0.8)	40 (13.2)	1 (0.3)
Dizziness	71 (11.8)	2 (0.3)	34 (11.2)	0 (0.0)
Muscle ache	71 (11.8)	3 (0.5)	17 (5.6)	0 (0.0)
Asthenia	65 (10.8)	6 (1.0)	20 (6.6)	2 (0.7)
Diarrhea	60 (10.0)	1 (0.2)	34 (11.2)	3 (1.0)
Influenza-like illness	58 (9.7)	0 (0.0)	11 (3.6)	0 (0.0)
Musculoskeletal pain	54 (9.0)	3 (0.5)	31 (10.2)	3 (1.0)
Dyspnea	52 (8.7)	11 (1.8)	14 (4.6)	3 (1.0)
Edema peripheral	50 (8.3)	1 (0.2)	31 (10.2)	1 (0.3)
Hot flush	49 (8.2)	2 (0.3)	29 (9.6)	1 (0.3)
Hematuria	46 (7.7)	6 (1.0)	18 (5.9)	3 (1.0)
Muscle spasms	46 (7.7)	2 (0.3)	17 (5.6)	0 (0.0)

(Table 1 continued on next page.)

Table 1 Incidence of Adverse Events Occurring in ≥5% of Patients Randomized to PROVENGE

	PROVENGE (N = 601)		Control* (N = 303)	
	All Grades n (%)	Grade 3-5 n (%)	All Grades n (%)	Grade 3-5 n (%)
Hypertension	45 (7.5)	3 (0.5)	14 (4.6)	0 (0.0)
Anorexia	39 (6.5)	1 (0.2)	33 (10.9)	3 (1.0)
Bone pain	38 (6.3)	4 (0.7)	22 (7.3)	3 (1.0)
Upper respiratory tract infection	38 (6.3)	0 (0.0)	18 (5.9)	0 (0.0)
Insomnia	37 (6.2)	0 (0.0)	22 (7.3)	1 (0.3)
Musculoskeletal chest pain	36 (6.0)	2 (0.3)	23 (7.6)	2 (0.7)
Cough	35 (5.8)	0 (0.0)	17 (5.6)	0 (0.0)
Neck pain	34 (5.7)	3 (0.5)	14 (4.6)	2 (0.7)
Weight decreased	34 (5.7)	2 (0.3)	24 (7.9)	1 (0.3)
Urinary tract infection	33 (5.5)	1 (0.2)	18 (5.9)	2 (0.7)
Rash	31 (5.2)	0 (0.0)	10 (3.3)	0 (0.0)
Sweating	30 (5.0)	1 (0.2)	3 (1.0)	0 (0.0)
Tremor	30 (5.0)	0 (0.0)	9 (3.0)	0 (0.0)

*Control was non-activated autologous peripheral blood mononuclear cells.

Cerebrovascular Events. In controlled clinical trials, cerebrovascular events, including hemorrhagic and ischemic strokes, were reported in 3.5% of patients in the PROVENGE group compared with 2.6% of patients in the control group.

(See Adverse Reactions [6] of full Prescribing Information.)

To report SUSPECTED ADVERSE REACTIONS, contact Dendreon Corporation at 1-877-336-3736 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Dendreon Corporation
Seattle, Washington 98101

Dendreon
Targeting Cancer, Transforming Lives®

P-A-11.10-073.01

PROVENGE®
(sipuleucel-T)

In asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer

PROVENGE is the first in a new class of therapy

that is designed to activate a patient's own antigen-presenting cells to stimulate an immune response against prostate cancer.

- **Extends median survival beyond 2 years**—25.8 months compared with 21.7 months for patients in the control* group (*P*=.032)
- **Reduction in risk of death—22.5%** (HR=0.775, 95% CI: 0.614, 0.979)
- **Therapy completed in 3 cycles**—3 infusions, at approximately 2-week intervals†
- **Most common adverse events are primarily mild or moderate**—chills, fatigue, fever, back pain, nausea, joint ache, and headache

*Control was nonactivated, autologous, peripheral blood mononuclear cells.
†The dosing interval ranged from 1 to 15 weeks in controlled clinical trials.

INDICATION: PROVENGE® (sipuleucel-T) is an autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.

IMPORTANT SAFETY INFORMATION: PROVENGE is intended solely for autologous use and is not routinely tested for transmissible infectious diseases.

In controlled clinical trials, serious adverse events reported in the PROVENGE group include acute infusion reactions (occurring within 1 day of infusion) and cerebrovascular events. Severe (Grade 3) acute infusion reactions were reported in 3.5% of patients in the PROVENGE group. Reactions included chills, fever, fatigue, asthenia, dyspnea, hypoxia, bronchospasm, dizziness, headache, hypertension, muscle ache, nausea, and vomiting. No Grade 4 or 5 acute infusion reactions were reported in patients in the PROVENGE group.

The most common adverse events (incidence ≥15%) reported in the PROVENGE group are chills, fatigue, fever, back pain, nausea, joint ache, and headache.

Please see Brief Summary of full Prescribing Information on the adjacent page.

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P-A-02.11-007.00

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PROVENGE®
(sipuleucel-T)
Stimulate a Response