

A SPECIAL MEETING REVIEW EDITION

**Highlights in Advanced Prostate Cancer From the
2012 ASCO Genitourinary Cancers Symposium**

February 2–4, 2012 • San Francisco, California

Special Reporting on:

- An Analysis to Quantify the Benefit of Sip-T Accounting for the Crossover in the Control Arm of the IMPACT Study
- Effect of MDV3100, an Androgen Receptor Signaling Inhibitor (ARSI), on Overall Survival in Patients With Prostate Cancer Postdocetaxel: Results From the Phase III AFFIRM Study
- Approved Agents and Related Trials in Castration-Resistant Prostate Cancer
- Optimal Sequencing of Agents in Castration-Resistant Prostate Cancer
- Novel Targets, Agents, and Trials in Castration-Resistant Prostate Cancer
- Sipuleucel-T Product Characterization Across Different Disease States of Prostate Cancer

PLUS Meeting Abstract Summaries

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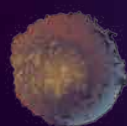
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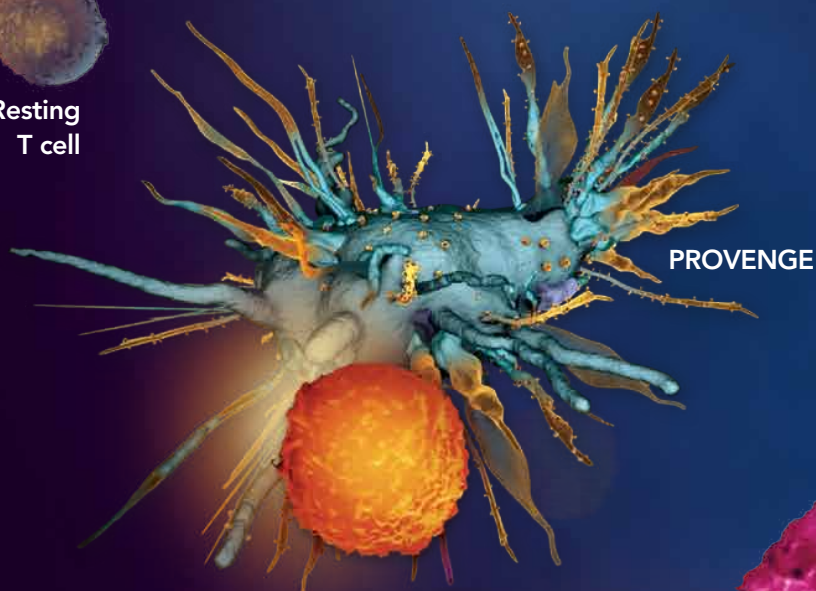
IN ADVANCED PROSTATE CANCER...

PROVENGE

**ACTIVATE THE POWER
OF THE IMMUNE SYSTEM.
EXTEND SURVIVAL.**

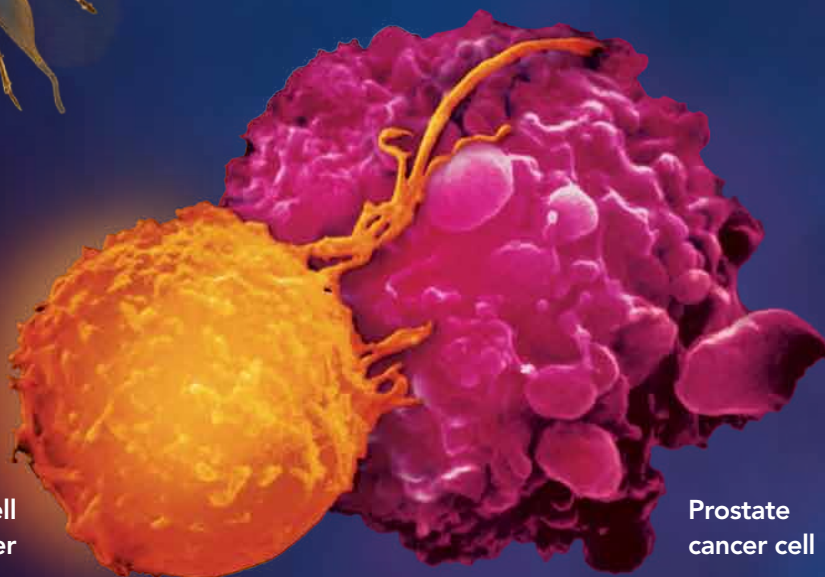


Resting
T cell



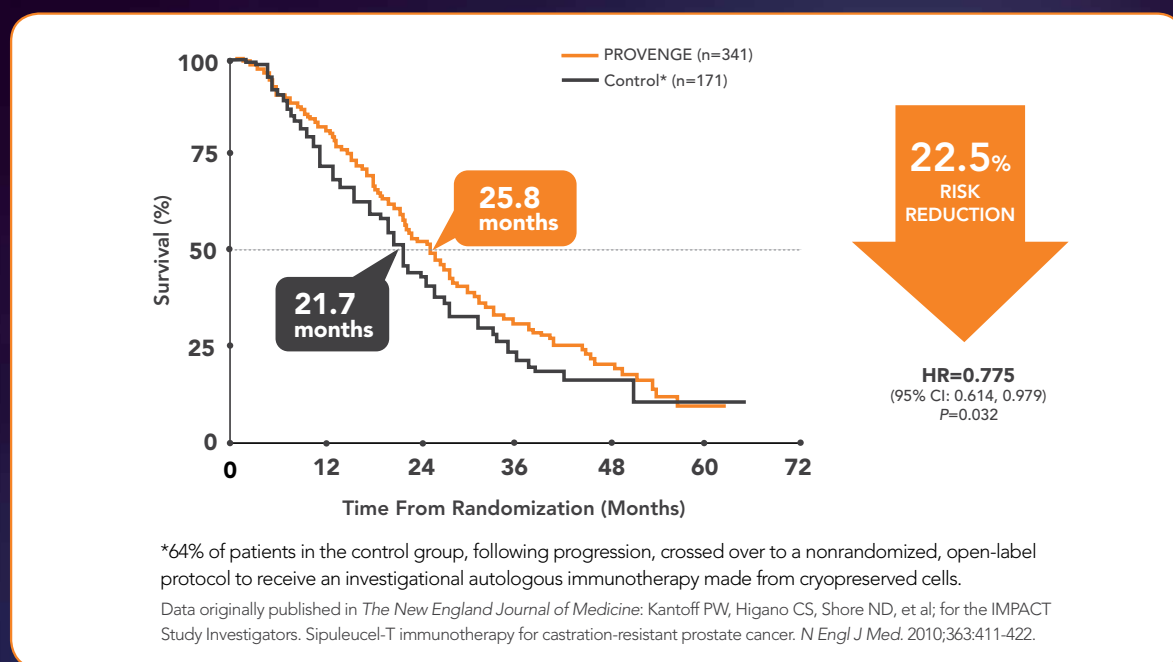
PROVENGE-activated T cell

Activated T cell
attacks prostate cancer



Prostate
cancer cell

OVERALL SURVIVAL BENEFIT OF PROVENGE^{1,2}



- **PROVENGE** extends median survival beyond 2 years¹
- Only 1.5% of patients treated with **PROVENGE** in the pivotal trial discontinued treatment due to adverse events²
 - The most common adverse events in **PROVENGE** trials were chills, fatigue, fever, back pain, nausea, joint ache, and headache²
- **PROVENGE** is the first and only FDA-approved immunotherapy for advanced prostate cancer
- The NCCN recommends **PROVENGE** as a *first-line* treatment for men with asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer (*NCCN Category 1 recommendation*)³

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 were chills, fatigue, fever, back pain, nausea, joint ache, and headache.

For more information on PROVENGE, please see Brief Summary of Prescribing Information on adjacent page.

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 autologous peripheral blood mononuclear cells.

The most common adverse events, reported in patients in the PROVENGE group at a rate $\geq 15\%$, 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 $\geq 5\%$ 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 $\geq 5\%$ 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 $\geq 5\%$ 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**

References: 1. 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.
2. PROVENGE [package insert]. Dendreon Corporation; June 2011.
3. NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer. V.4.2011. National Comprehensive Cancer Network Web site. www.nccn.org. Accessed October 24, 2011.

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Targeting Cancer, Transforming Lives®

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PROVENGE®
(sipuleucel-T)

An Analysis to Quantify the Benefit of Sip-T Accounting for the Crossover in the Control Arm of the IMPACT Study

Three phase III trials have demonstrated a longer overall survival (OS) with sipuleucel-T in men with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (CRPC) compared to controls who received nonactivated autologous cell products.¹⁻³ However, the results of these trials may have been confounded by the option for patients in the control arm who experienced disease progression to receive salvage therapy with APC8015, an autologous immunotherapy made from cells cryopreserved at the time of control generation. A previous analysis of data from the 3 phase III trials suggested that crossover treatment may have prolonged OS in the control arm (hazard ratio [HR], 0.52; 95% confidence interval [CI], 0.37–0.73; $P=0.0001$).⁴ However, patients in the control arm who received the crossover treatment had more favorable prognostic characteristics than those who did not. Therefore, an exploratory analysis was undertaken to investigate the potential contribution of crossover APC8015F treatment on the OS of the control group in the IMPACT (Immunotherapy for Prostate Adenocarcinoma Treatment) trial.⁵ The double-blind, placebo-controlled, multicenter, phase III IMPACT trial enrolled patients with asymptomatic or minimally symptomatic metastatic CRPC.¹ Patients were randomized 2:1 to receive 3 infusions of biweekly

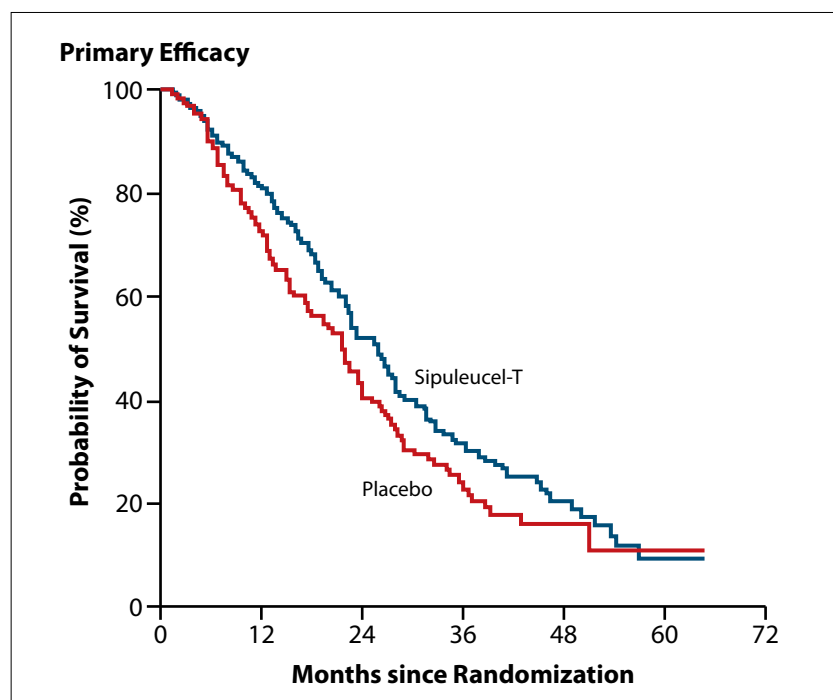


Figure 1. Kaplan-Meier estimate of overall survival in the IMPACT trial. Improvement is seen with sipuleucel-T compared with placebo. IMPACT=Immunotherapy for Prostate Adenocarcinoma Treatment. Adapted from Kantoff et al. *N Engl J Med*. 2010;363:411-422.

sipuleucel-T or control therapy. After objective disease progression, patients in the control arm were offered 3 infusions of APC8015F through an open-label, nonrandomized protocol.

OS, the primary endpoint, was analyzed using a 2-sided Wald test for sipuleucel-T treatment effect. A rank-preserving structural failure time model was applied to adjust the estimate of OS prolongation by correcting for the effects of crossover treatment.

The analysis assumed a Weibull distribution in an accelerated failure time model to generate the HR for the treatment effect. The IMPACT study randomized 341 patients to sipuleucel-T treatment and 171 patients to the control arm. After completing study treatment, 63.7% of patients in the control arm received subsequent APC8015F. The crossover treatment constituted the first salvage intervention for 49.1% of patients in the control arm.

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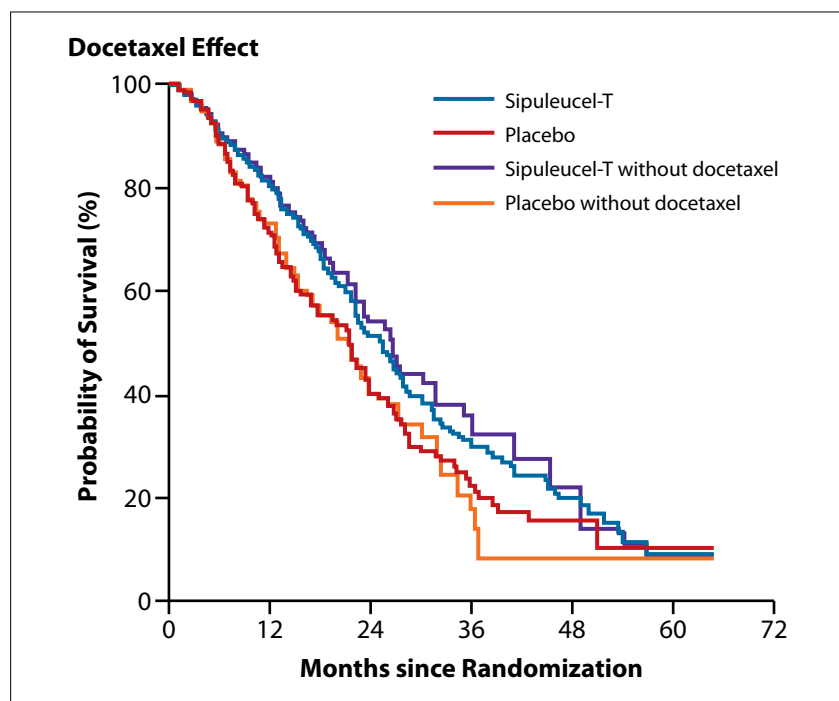


Figure 2. Kaplan-Meier estimate of overall survival in the IMPACT trial, with adjustment for use of docetaxel treatment after study therapy. IMPACT=Immunotherapy for Prostate Adenocarcinoma Treatment. Adapted from Kantoff et al. *N Engl J Med.* 2010;363:411-422.

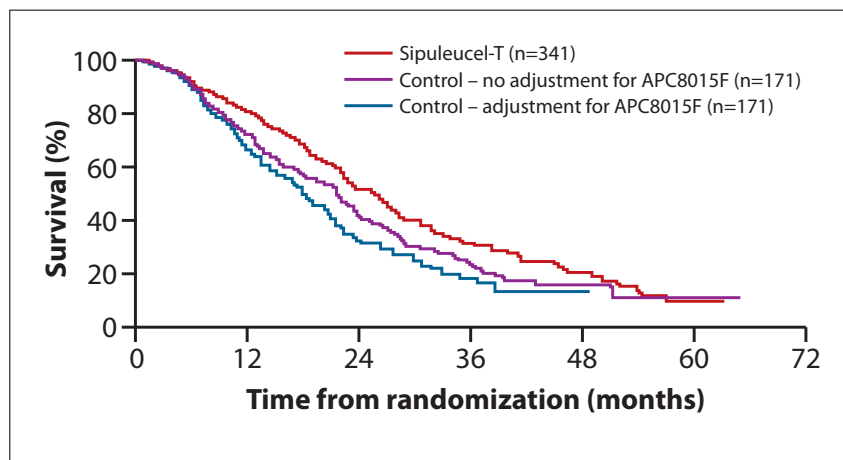


Figure 3. An exploratory analysis of data from the IMPACT trial found that the survival improvement observed in the sipuleucel-T arm was increased after adjustment for the use of APC8015F. IMPACT=Immunotherapy for Prostate Adenocarcinoma Treatment. Adapted from Nabhan et al. *J Clin Oncol* (ASCO Genitourinary Cancers Symposium Abstracts). 2012;30(suppl 5): Abstract 144.

In randomized, controlled studies of sipuleucel-T, patients in the control arm who received APC8015F treatment had more favorable baseline characteristics, such as ECOG (Eastern

Cooperative Oncology Group) performance status, prostate-specific antigen (PSA) level, alkaline phosphatase level, and number of bone metastases, compared to control patients who did

not receive APC8015F and patients randomized to sipuleucel-T. However, baseline characteristics were well balanced between the 2 treatment arms in the IMPACT trial.¹

The IMPACT trial originally reported a median improvement in OS of 4.1 months with sipuleucel-T treatment, showing a median OS of 25.8 months versus 21.7 months for the control arm (HR, 0.78; 95% CI, 0.61–0.98; $P=.032$; Figure 1). Median OS was 23.8 months for those who received crossover treatment ($n=109$) and 11.6 months for those who did not ($n=62$). The treatment effect was still evident after adjustment for use of docetaxel after the study therapy (Figure 2).

Because patients in the control arm of the IMPACT trial who received APC8015F had more favorable baseline characteristics,⁴ a series of analyses that adjusted for baseline and post-progression covariates was performed. Based on these revised analyses, the improved postprogression survival of patients treated with APC8015F persisted. Cumulative CD54 upregulation, reflecting antigen-presenting cell upregulation, was also correlated with survival in patients who received crossover treatment. This correlation is similar to that observed in patients treated with sipuleucel-T. Further evidence of APC8015F crossover treatment efficacy was suggested by an increased incidence of the most common adverse events, including the frequency of infusional toxicities, in patients who received crossover treatment compared with control arm patients who did not.⁴ Collectively, these findings demonstrate evidence of APC8015F clinical activity.

By invoking the rank-preserving structural failure time model and assuming that APC8015F treatment was equally effective as sipuleucel-T treatment, the current analysis reconstructed the control arm survival curve as if no patients in the control arm had received the crossover treatment. This new analysis yielded a median OS esti-

mate of 18.0 months for the control arm (HR, 0.60; 95% CI, 0.41–0.96), thus revealing an improvement in median OS of 7.8 months for treatment with sipuleucel-T (Figure 3).

Further analyses using the rank-preserving structural failure time model and assuming that crossover treatment was less effective than the sipuleucel-T treatment resulted in median OS estimates of 7.0 months (HR, 0.64; 95% CI, 0.44–0.97), 6.0 months (HR, 0.68; 95% CI, 0.49–0.97), 5.1 months (HR, 0.73; 95% CI, 0.55–0.97),

and 4.1 months (HR, 0.77; 95% CI, 0.61–0.98), assuming an efficacy of 75%, 50%, 25%, or 0% for crossover treatment. The adjusted analyses indicate that the treatment effect with sipuleucel-T in the IMPACT trial may have been greater than originally reported.

References

1. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med*. 2010;363:411–422.
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placebo-controlled, phase 3 trials of active cellular immunotherapy with sipuleucel-T in advanced prostate cancer. *Cancer*. 2009;115:3670–3679.

3. Small EJ, Schellhammer PF, Higano CS, et al. Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic, asymptomatic hormone refractory prostate cancer. *J Clin Oncol*. 2006;24:3089–3094.

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5. Nabhan C, Gomella LG, DeVries T, et al. An analysis to quantify the overall survival (OS) benefit of sipuleucel-T accounting for the crossover in the control arm of the IMPACT study. *J Clin Oncol* (ASCO Genitourinary Cancers Symposium Abstracts). 2012;30(suppl 5): Abstract 144.

Effect of MDV3100, an Androgen Receptor Signaling Inhibitor (ARSI), on Overall Survival in Patients With Prostate Cancer Postdocetaxel: Results From the Phase III AFFIRM Study

Scher presented results from the phase III AFFIRM (Safety and Efficacy Study of MDV3100 in Patients With Castration-Resistant Prostate Cancer Who Have Been Previously Treated With Docetaxel-based Chemotherapy) trial.¹ This randomized, double-blind, placebo-controlled, multinational study evaluated MDV3100 in men with CRPC whose disease had progressed on docetaxel. Patients were randomized 2:1 to receive MDV3100 (160 mg daily; n=800) or matched placebo (n=399). Use of glucocorticoids was permitted. The primary endpoint was OS. The trial was conducted at 156 centers in 15 countries. Secondary endpoints indicating response to treatment included PSA response, soft tissue objective response, Functional Assessment of Cancer Therapy-Prostate Quality of Life response, pain palliation, and levels of circulating tumor cells. Secondary endpoints indicating disease progression included radiographic progression-free survival (PFS), time to PSA progression, and time to first skeletal-related event. Patient baseline characteristics were well balanced between the 2 arms, both in

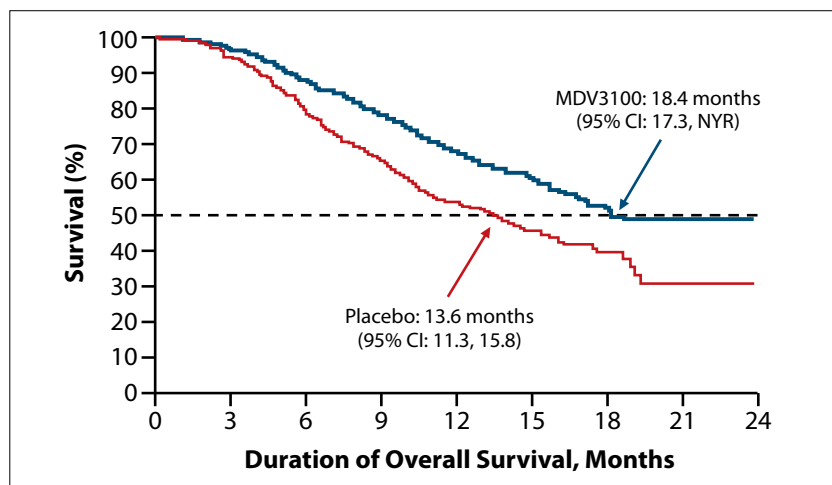


Figure 4. In the AFFIRM trial, treatment with MDV3100 prolonged median overall survival as compared with placebo. AFFIRM=Safety and Efficacy Study of MDV3100 in Patients With Castration-Resistant Prostate Cancer Who Have Been Previously Treated With Docetaxel-based Chemotherapy. Adapted from Scher et al. *J Clin Oncol* (ASCO Genitourinary Cancers Symposium Abstracts). 2012;30(suppl 5): Abstract LBA1.

terms of patient demographics and disease characteristics.

The planned interim analysis was conducted after 520 deaths were reached on September 25, 2011. The analysis led the independent data monitoring committee to conclude that a statistically significant and clinically

meaningful OS benefit had occurred. As a result, the committee determined that the study should be halted and unblinded and that patients in the control arm should be offered treatment with MDV3100.

Based on the interim analysis, treatment with MDV3100 prolonged median

OS by 4.8 months relative to placebo, yielding a median OS of 18.4 months with MDV3100 treatment (95% CI, 17.3 months–not yet reached) versus 13.6 months with placebo (95% CI, 11.3 months–15.8 months; Figure 4). A 37% reduction in the risk of death was associated with MDV3100 (HR, 0.631; 95% CI, 0.529–0.752; $P=.0001$). Forest plot analysis showed a benefit androgen receptor signaling blockage treatment across virtually all subgroups. The subgroups of patients with ECOG performance status of 2 or who had received 2 or more prior chemotherapies showed HRs of 0.65 (95% CI, 0.39–1.07) and 0.74 (95% CI, 0.54–1.03), respectively, but both of these subgroups had small numbers of patients.

Secondary outcomes underscored the benefit from MDV3100 treatment. PSA levels declined by at least 50% from baseline in 54.0% of patients treated with MDV3100 versus 1.5% in the placebo arm ($P<.0001$), and they

declined by at least 90% in 24.8% versus 0.9% of patients, respectively ($P=.0001$). Median time to PSA progression favored MDV3100 treatment (8.3 months vs 3.0 months; HR, 0.248; 95% CI, 0.204–0.303; $P<.0001$). Computed tomography/magnetic resonance imaging with Response Evaluation Criteria In Solid Tumors (RECIST) evaluation revealed a significant increase in soft tissue response rate with study drug treatment (28.9% vs 3.8%; $P<.0001$). Similarly, the median time to radiographic PFS was 8.3 months with MDV3100 versus 2.9 months with placebo (HR, 0.404; 95% CI, 0.350–0.466; $P<.0001$).

MDV3100 was well tolerated with respect to adverse events. Fatigue was the most common adverse event of any grade, occurring in 33.6% of patients in the MDV3100 treatment arm and 29.1% in the control arm, and was the most common event of grade 3 or greater, occurring at 6.3% for MDV3100 versus 7.3% for placebo. The data showed very

similar rates of cardiac disorders, including myocardial infarction, and similar rates of abnormal liver function tests. In the MDV3100 arm, 5 patients (0.6%) experienced seizures, all of which were grade 3 or higher. No patients in the control arm experienced a seizure. Of note, MDV3100 did not induce myelosuppression, and no patients died on study treatment. The investigators concluded that the trial efficacy data and favorable safety profile support the use of MDV3100 as first-line treatment for advanced CRPC patients with previous docetaxel treatment.

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Approved Agents and Related Trials

Dr. Gary MacVicar discussed approved agents for CRPC during a General Session.¹ In 2004, docetaxel made history as the first systemic agent approved by the FDA that improved OS in men with metastatic CRPC.² More recently, 3 other agents that extend OS have been approved: abiraterone, sipuleucel-T, and cabazitaxel. Of note, all 3 agents have a different mechanism of action. In addition, denosumab is available for supportive care for skeletal-related events.

Hormonal Therapies

Preclinical studies have suggested that, despite androgen-deprivation therapy, progressive prostate cancer may be driven by paracrine mechanisms involving the androgen receptor. Abiraterone is an oral inhibitor of CYP17A, an enzyme involved in androgen synthesis.

By inhibiting both the 17- α hydroxylase and 17,20 lyase activity of the enzyme, abiraterone reduces testosterone production, decreasing androgen production in adrenal, prostate, and tumor tissues. A phase III trial of men with metastatic CRPC who had previously received docetaxel randomized patients to either abiraterone plus prednisone or to placebo plus prednisone. Median OS improved to 14.8 months for patients who received abiraterone versus 10.9 months for placebo (HR, 0.65; 95% CI, 0.54–0.77; $P=.001$; Figure 5).³ Abiraterone is generally well tolerated, although fluid retention, hypokalemia, and hypertension have been observed and may be related to mineralocorticoid excess. A phase III trial in docetaxel-naïve patients has accrued patients, and results are pending.

TAK-700 also inhibits androgen synthesis.⁴ This agent is being studied

in an ongoing phase III trial in pre- and postdocetaxel patients. MDV3100 is an oral androgen receptor antagonist that disrupts nuclear translocation of the receptor and subsequent DNA binding, thus inhibiting androgen-regulated gene expression. In a phase III study of patients previously treated with docetaxel, OS improved from 13.6 months with placebo to 18.4 months with MDV3100 (HR, 0.631; 95% CI, 0.529–0.752; $P=.0001$).⁵

Cabazitaxel is a novel taxane that showed activity in preclinical studies of taxane-resistant models and in early studies of patients with docetaxel-refractory disease. The recommended dose was 20 mg/m², and the dose-limiting toxicity was neutropenia. In a phase III study, men with metastatic CRPC and previous progression on docetaxel were randomized to receive daily prednisone plus either

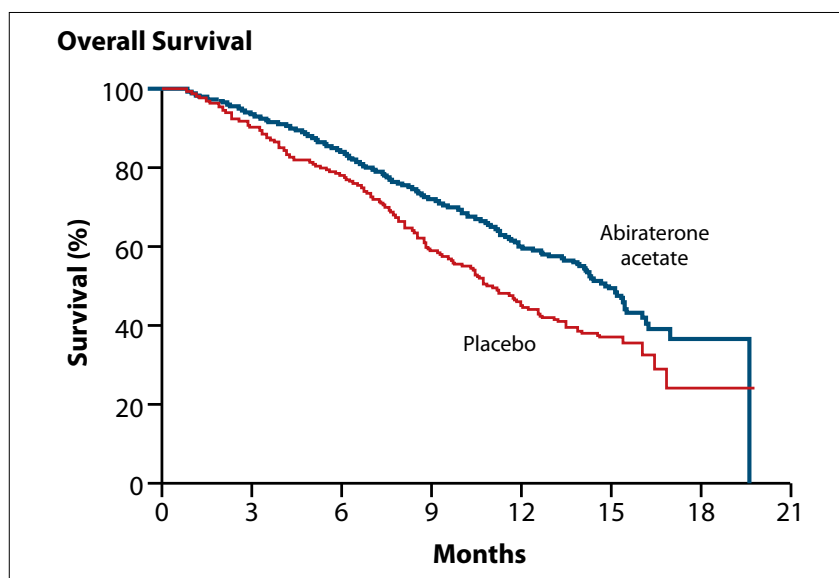


Figure 5. Data from a phase III trial of men with metastatic castration-resistant prostate cancer showed that median overall survival was improved with abiraterone as compared with placebo. Adapted from de Bono et al. *N Engl J Med.* 2011;364:1995-2005.

mitoxantrone (12 mg/m²; n=377) or cabazitaxel (25 mg/m²; n=378) every 3 weeks.⁶ After a median follow-up of 13.7 months, cabazitaxel produced a superior median OS of 15.1 months (vs 12.7 months; HR, 0.70; 95% CI, 0.59–0.83; *P* < .0001), but was also associated with higher rates of grade 3/4 febrile neutropenia and diarrhea. Of the patients treated with cabazitaxel, 7.5% had febrile neutropenia of grade 3 or higher compared with 1.3% of patients in the control arm. Diarrhea of any grade occurred in 46.6% of patients treated with cabazitaxel versus 10.5% of control arm patients, whereas diarrhea of at least grade 3 occurred in 6.2% of cabazitaxel-treated patients versus 0.3% of control-arm patients.

Given the global nature of the study, it is possible that supportive care varied. Additionally, prophylactic treatment with granulocyte colony-stimulating factor is possible for patients at higher risk for neutropenia. However, in light of the associated toxicities, cabazitaxel may currently best be reserved for patients with a good performance status. The phase III PROSELICA (Cabazitaxel at 20 mg/m² Compared to 25 mg/m² With Prednisone for the

Treatment of Metastatic Castration Resistant Prostate Cancer) trial will provide further insights into the drug's safety, efficacy, and optimal dosing.⁷

Immunotherapy

Sipuleucel-T is an autologous antigen-presenting cell vaccine. The patient's mononuclear cells are collected via leukapheresis and exposed to a recombinant fusion protein, PA2024, encompassing prostatic acid phosphatase and granulocyte/macrophage colony-stimulating factor. The activated cells are then infused into the patient intravenously. The treatment is performed 3 times at 2-week intervals. The treated antigen-presenting cells are believed to stimulate T cells to mount an immune response against the prostate cancer cells. In a phase III trial with OS as the primary endpoint, men with asymptomatic or minimally symptomatic metastatic CRPC, but no visceral disease, were randomized to either sipuleucel-T or placebo.⁸ Sipuleucel-T prolonged OS to 25.8 months (vs >21.7 months with placebo; HR, 0.78; 95% CI, 0.61–0.98; *P* = .03). No differences in PSA response rates or time to

progression were recorded, suggesting that PSA response or radiographic progression may not reflect treatment efficacy of sipuleucel-T.

Other immunotherapies in development include PROSTVAC-VF and ipilimumab. PROSTVAC-VF is a vaccine based on the pox virus; it encodes PSA and 3 immune costimulatory molecules. A randomized, placebo-controlled, phase II trial failed to show improvement in the primary endpoint of PFS, but yielded an improved OS of 25.1 months (vs 16.6 months; HR, 0.56; 95% CI, 0.37–0.85; *P* = .0061).⁹ A phase III trial is in progress in men with asymptomatic or minimally symptomatic metastatic CRPC. Ipilimumab is an antibody that binds to CTLA4 and activates T-cell anti-tumor activity. Early studies with ipilimumab have yielded a PSA response rate of 22%.¹⁰ Randomized phase III studies with this antibody in the pre- and post-docetaxel settings are ongoing.

Bone-Targeted Therapy

Bone metastases occur in the majority of metastatic CRPC patients and often cause morbidity. Tumors secrete growth factors into the bone tissue, causing stromal cells and osteoblasts to secrete the receptor activator of NF-κB ligand (RANKL), which is normally expressed on the surface of stromal cells and osteoblasts. The “vicious cycle” involves crosstalk among prostate tumor cells, osteoblasts, and osteoclasts, mediated by cytokines, such that bone resorption ultimately leads to increased expression of RANKL, and hence osteoclastogenesis.

Denosumab is a monoclonal antibody that binds to RANKL and thus may disrupt the cytokine signaling that supports bone metastases. In a placebo-controlled phase III study that randomized patients with metastatic CRPC to receive either denosumab (120 mg) or zoledronic acid (4 mg), denosumab conferred a 3.6-month extension in the time to a first skeletal-related event

(20.7 months vs 17.1 months; HR, 0.82; 95% CI, 0.71–0.95; $P=.008$ for superiority; $P=.0002$ for non-inferiority; Figure 6).¹¹ No difference in OS or time to progression was revealed. A higher rate of hypocalcemia was observed with denosumab treatment (13% vs 6%; $P<.0001$), indicating the need for vitamin D supplementation for patients receiving the antibody therapy. The rates of osteonecrosis of the jaw were similar and low for both treatment arms.

For patients with androgen-sensitive disease, denosumab appears to have a positive impact on lumbar spine density as well as risk for vertebral fractures. In a double-blind, multicenter study of men with nonmetastatic CRPC, positive changes in lumbar spine density at 24 months occurred (5.6% vs -1.0%; $P=.001$) and the rate of new vertebral fractures was lower (1.5% vs 3.9%; $P=.006$) in patients receiving denosumab relative to placebo.¹² In a phase III trial, denosumab increased bone-metastasis-free survival by a median of 4.3 months relative to placebo (29.5 months vs 25.2 months; HR, 0.85; 95% CI, 0.73–0.98; $P=.028$).¹³ No difference in OS was recorded, and denosumab treatment was associated with increased risk of osteonecrosis of the jaw and hypocalcemia, consistent with the known toxicity profile of denosumab. The FDA has approved denosumab for osteoporosis prophylaxis in the androgen-sensitive setting but not yet for delaying bone metastases in men with nonmetastatic CRPC.

Radiopharmaceuticals are small molecules that deliver focal radiation to bone metastases. Strontium-89 and samarium-153 are beta-emitters, and both are FDA-approved for palliation of bone pain in metastatic CRPC. Radium-223 is currently in development for treating bone metastases. As a beta-emitter, it can deliver more localized radiation with higher energy, thus causing less damage to surrounding tissues. A phase III trial examined radium-223 versus placebo

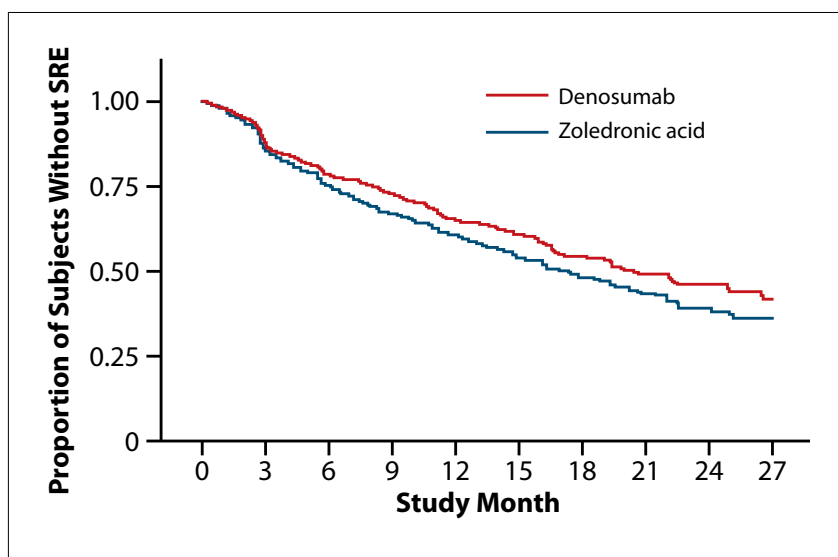


Figure 6. In a placebo-controlled phase III study that randomized patients with metastatic castration-resistant prostate cancer to receive either denosumab (120 mg) or zoledronic acid (4 mg), denosumab conferred an advantage. Adapted from Fizazi et al. *Lancet*. 2011;377:813-822.

in men with symptomatic metastatic CRPC and bone metastases who were either unfit for docetaxel or had progressed on docetaxel.¹⁴ Treatment with radium-223 yielded an improvement in OS from 11.2 months to 14 months (HR, 0.695; $P=.00185$) relative to placebo, and toxicity from radium-223 was manageable.

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Optimal Sequencing of Agents in Castration-Resistant Prostate Cancer

In a General Session, Dr. Philip Kantoff discussed sequencing of agents in CRPC.¹ The FDA has recently approved 4 new therapies for the treatment of men with CRPC: cabazitaxel,² sipuleucel-T,³ abiraterone,⁴ and denosumab.⁵ Several other agents have the potential to be approved in the next few years, including radium-223 chloride, MDV3100, and others, and new indications are likely to be granted for established agents. Abiraterone may extend its indication into docetaxel-naïve men. Denosumab is also used, although not yet approved, for the prevention of skeletal-related events in patients with bone metastases.

Sequencing strategies with the available agents have yet to be established. Thus, therapeutic choice is typically guided by toxicity, perceived patient benefit, ease of administration, and the design of registration trials. A more rational approach is needed that incorporates the selection of patients more likely to benefit and the knowledge of how different treatments may interact to augment or diminish their respective activities. Dr. Kantoff emphasized that data directing optimal sequential treatment programs are lacking. Nonetheless, it is possible to begin to construct a rational framework.

Few patients with advanced prostate cancer are cured with existing androgen deprivation therapy. Anecdotal long-term

survivals with docetaxel exist, but they are very rare. Great strides have been made in recent years in identifying new and effective agents, as well as in validating new mechanisms. Remarkably, immunotherapy has been shown to prolong survival in some metastatic CRPC patients, as evidenced by data from clinical trials with sipuleucel-T.⁶ Bone-targeting agents can prolong survival as well.⁷ As has been known for the last 20 years, androgen signaling is central to tumor growth in CRPC. Thus, perhaps less surprising is the recent findings that reducing androgen signaling with abiraterone or MDV3100 can prolong survival.^{8,9}

Curing men with CRPC using new agents, either in sequence or in combination, will be rare. A realistic goal, however, is to cure patients with early stage, intermediate- and high-risk, localized disease, and to this end, combination therapies may prove valuable. Although this aim obviously represents a daunting task for pharmaceutical companies, exploration of therapeutic combinations is essential for moving treatment forward and should be a major focus of the research agenda.

The impact of current androgen-deprivation therapy is modest in men with advanced prostate cancer. Trials that optimize androgen-deprivation therapy earlier in the disease should be encouraged. More robust androgen blockade has been observed from combinations of traditional agents with newer agents. Immunotherapy and bone targeting may have more substantial effects earlier in the disease, but these concepts need to be proven with level 1 evidence before becoming the standard of care. Similarly, clinical trials are needed to demonstrate whether the use of cytotoxic agents, such as docetaxel and cabazitaxel, can confer survival benefits in patients with CRPC.

The current treatment framework divides patients into pre- and postdocetaxel

ABSTRACT SUMMARY Analysis of 45 Patients Pretreated With Sipuleucel-T (SIP-T) in a Community Practice

Shah and associates presented their observations of toxicity with sipuleucel-T in a community practice since the treatment's approval in May 2010 (Abstract 94). One hundred patients were eligible for sipuleucel-T treatment; these patients had minimally symptomatic or asymptomatic metastatic CRPC and limited or no visceral metastases, and they were not currently receiving chemotherapy. Fifty-five patients were treated. Compared to the treated group, the untreated patients showed older age, higher ECOG scores, higher PSA, and other characteristics consistent with their untreated status. Prior systemic therapies in the treated group included antiandrogens (93%), estrogens (33%), chemotherapy (31%), and abiraterone (20%). Thirty-two patients received central lines. Of the first 17 patients, 10 had tunneled lines. One patient was hospitalized for 10 days for methicillin-resistant *Staphylococcus aureus* infection; 2 patients were delayed due to technical issues relating to the tunneled lines; and all 10 patients voiced concerns about the complexity of tunneled line care. Subsequently, 22 patients with central lines had external jugular lines placed by interventional radiology, which were removed the same day, and no line complications were observed thereafter. One patient who had received prior treatment with samarium and external radiation therapy had too few cells for treatment. Two patients underwent a fourth pheresis for technical issues. One patient, who was not premedicated, had marked rigors after the second infusion. After a median follow-up of approximately 10 months, no other adverse reactions greater than grade 1 were noted during or after sipuleucel-T treatment. Eighteen percent of patients were still taking low-dose steroids during treatment. No vascular events occurred. Six treated patients (13%) died of progressive disease, 3 within 30 days. Eleven untreated patients (18%) died of progressive disease.

groups. However, this concept may not be clinically valid. Post-docetaxel patients certainly have more advanced disease, and they generally respond less well to most treatment, particularly chemotherapy. However, this reduced response is not observed in all studies of postdocetaxel patients. It is not known whether treatment with other agents, such as sipuleucel-T or abiraterone, makes a patient more or less likely to respond to docetaxel, although some studies suggest that patients previously treated with either sipuleucel-T or ketoconazole respond as well to docetaxel as control patients. Although the pre- and postdocetaxel divisions most likely represent boundaries necessitated by regulatory procedures rather than biologic boundaries, studies are needed to address this issue.

The definition of the CRPC state needs to be updated. A rising level of PSA, based on Prostate Cancer Working Group criteria, is probably reasonable; however, the serum testosterone of 50 ng/dL must be reevaluated. Moreover, serum testosterone may not accurately reflect whether a patient is truly ligand dependent, and intratumoral testosterone may provide a superior measure of ligand dependency. Major advances in functional and other forms of imaging are also needed to accurately redefine CRPC.

Thoughts on Sequencing

In nonmetastatic CRPC, no therapy has been shown to improve survival. Ideally, these patients should be entered into clinical trials. For patients with a slow PSA velocity, observation is reasonable. Secondary hormonal therapies may be considered, such as ketoconazole, estrogens, and alternative anti-androgens. However, there is no level 1 evidence to show that these treatments are in fact effective. Emerging androgen signaling inhibitors and immunotherapy may prove useful, but again, level 1 evidence is lacking.

Bone protection is extremely important for every patient with metastatic

ABSTRACT SUMMARY Evaluation of Immune Activation Following Neoadjuvant Sipuleucel-T in Subjects With Localized Prostate Cancer

An open-label, phase II trial (P07-1) enrolled subjects with prostate cancer to receive 3 infusions of sipuleucel-T at intervals of approximately 2 weeks beginning 6–7 weeks prior to radical prostatectomy. Results were presented by Sheikh (Abstract 178). Before and after ex vivo culture with PA2024, all subject samples were evaluated for cellular composition and protein C activation; culture supernatant was examined for the presence of cytokines; and T-cell and B-cell activation was evaluated via flow cytometry. The 42 enrolled subjects had a median age of 61 years. Of these, 38 received all 3 infusions of sipuleucel-T. Activated protein C, based on CD54 upregulation, was greater at the second and third infusions relative to the first infusion. The proportion of CD4+ and CD8+ T cells did not change with treatment. However, the expression of markers of early T-cell activation, including CD134, CD137, CD278, and CD279, was greater in preculture cells obtained after the first infusion and increased further postculture. Similarly, although the percentage of B cells did not change, a progressive increase of memory B cells (CD20+, CD27+, IgD-, CD86+) was observed after the first infusion, before and after culture. Activated mature B cells (CD20+, CD27+, IgD+, CD86+) increased after culture. Levels of tumor necrosis factor- α , interferon- γ , and interleukin 2 were significantly elevated ($P < .001$ for each) in the second and third products. The investigators noted that the patterns observed with the second and third infusions, relative to the first infusion, are consistent with an immunologic “prime-boost” profile.

CRPC. Zoledronic acid and denosumab represent equally attractive options, although a modest improvement in efficacy is associated with denosumab and is supported by the National Comprehensive Cancer Network guidelines.¹⁰ Importantly, the optimal scheduling of these bone-protective agents has not been determined, and administration of these drugs is highly variable among different practices. Further data are required regarding the optimal timing of administration and consideration for individualized treatment. Patients with poor dentition should perhaps not receive these drugs at all given the association with osteonecrosis of the jaw. Other factors to consider when individualizing treatment include renal function, costs, copayments, and patient convenience with respect to scheduling and intravenous versus subcutaneous delivery. It is also possible that newer agents, such as abiraterone and MDV3100, are associ-

ated with less bone turnover than older agents, in which case bone loss prevention will become a less pressing matter. Data addressing this scenario are needed.

CRPC is clearly not one disease. Currently, patients are roughly categorized based on PSA velocity or PSA doubling time and the rapidity of objective changes. However, genotypic information is crucial to distinguish subtypes of CRPC and to accurately guide treatment. Patients with asymptomatic disease and a slower rate of progression should initially be considered for treatment with sipuleucel-T. Next, hormonal therapies, including ketoconazole and antiandrogens, should be considered. Abiraterone is the next agent to consider, although insurance reimbursement varies widely among states. Finally, enrollment in a clinical trial should be considered.

For asymptomatic, chemotherapy-naïve metastatic CRPC patients with a rapid rate of progression, sipuleucel-T

is not appropriate because responses may be delayed for many months. Hormonal therapies may be considered, although their efficacy is questionable. Abiraterone may be considered if it is covered by insurance, and clinical trials are a reasonable option. Finally, docetaxel may be considered, although it is more likely to be appropriate for patients with symptomatic disease.

For symptomatic, chemotherapy-naïve patients, docetaxel is the best option. For patients whose disease responded previously to docetaxel, a second course of docetaxel is an option after a treatment hiatus. However, docetaxel-resistant patients may be considered for abiraterone, which in light of its superior tolerability is preferable over further chemotherapy. Other treatment options include cabazitaxel and clinical trials, which are an excellent option for

these patients. Mitoxantrone remains an option, although its use has declined significantly with the introduction of newer agents. Sipuleucel-T is appropriate only for patients with a good prognosis and with low-volume, asymptomatic disease. In cases where the time required to obtain insurance approval for abiraterone may delay treatment, docetaxel may be given first, followed by abiraterone. New therapies, including sipuleucel-T, MDV3100, abiraterone, and radium-223 chloride will make it possible to treat elderly patients who are not eligible for chemotherapy.

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Novel Targets, Agents, and Trials

Dr. Evan Yu discussed novel targets and agents in a General Session.¹ There are many new cancer agents under investigation for prostate cancer representing a wide range of targets and mechanisms. Anti-angiogenic agents have shown impressive results in some cancer types but have yet to show an improvement in OS for men with prostate cancer. In a phase III trial, bevacizumab was examined in combination with docetaxel and prednisone versus docetaxel and prednisone alone for prostate cancer.² The bevacizumab patients experienced improvements in PFS, but not in OS. In a phase III trial of postdocetaxel patients, a regimen of sunitinib plus prednisone was compared with prednisone alone.³ Again, this trial showed a PFS benefit but no improvement in OS. Lenalidomide was evaluated in combination with docetaxel in the international, phase III MAINSAIL (Study to Evaluate Safety and Effectiveness of Lenalidomide in Combination With Docetaxel and Prednisone for Patients With Castrate-

Resistant Prostate Cancer) trial,⁴ but the trial was halted by the independent monitoring committee because the regimen failed to demonstrate superior OS, the primary endpoint. Aflibercept, also known as vascular endothelial growth factor (VEGF) trap, is under investigation as first-line combination treatment in the placebo-controlled, phase III VENICE (Aflibercept in Combination With Docetaxel in Metastatic Androgen Independent Prostate Cancer) trial, with a primary endpoint of OS.⁵ A planned interim analysis revealed no safety concerns, and the study is continuing as originally planned. Tasquinimod is a small molecule with antiangiogenic properties, although its exact mechanism of action is unknown. It is the subject of an ongoing phase III study.⁶ The trial is recruiting patients with asymptomatic to mildly symptomatic metastatic CRPC and will randomize 1,200 patients 2:1 to receive either tasquinimod (0.25 mg, 0.5 mg, or 1 mg daily) or placebo. The primary endpoint is PFS.

Cabozantinib

Cabozantinib (XL184) is a broad-spectrum, multikinase inhibitor that targets VEGFR2 and MET; however, it also inhibits RET, KIT, AXL, and other molecules. MET is highly expressed in prostate tumors with higher Gleason grades and in bone metastases.⁷ In prostate cancer, the androgen receptor represses MET expression, whereas androgen deprivation increases MET expression. Moreover, androgen deprivation also increases stromal and tumor expression of hepatocyte growth factor—the ligand for MET—thus creating a feedback loop that enhances MET signaling.

In a phase II randomized discontinuation trial, metastatic CRPC patients were given daily cabozantinib (100 mg) during a 12-week lead-in stage.⁸ The primary endpoint was overall response rate. Of the 108 patients with evaluable bone metastatic CRPC, 19% had complete resolution of all lesions, 56% had partial resolution of bone lesions, and 21%

had stable disease. Only 3% of patients showed disease progression, based on new lesions via bone scan. Declines in osteoblast and osteoclast activity were also observed for most patients. Post-hoc analyses suggested that patients experienced reductions in bone pain, with pain improvement noted at week 6 or week 12 in 67% of patients. Of 67 patients using narcotics for bone pain at baseline, 70% experienced pain improvement at week 6 or 12. Fifty-six percent of 55 evaluable patients were able to decrease or discontinue narcotics use.

Fifty-one percent of patients required at least 1 dose reduction due to adverse events. Specific adverse events of any grade included fatigue (63%), decreased appetite (49%), diarrhea (46%), and nausea (44%). Grade 3 events included fatigue (16%), decreased appetite (5%), nausea (4%), and diarrhea (2%). There were no grade 4 events, but 1 patient experienced a treatment-related grade 5 event.

Efforts are under way to discover efficacious yet more tolerable doses of cabozantinib. A dose-finding study examined metastatic CRPC patients in 2 cohorts that received cabozantinib doses of either 40 mg daily or 20 mg daily. At 6 weeks, no patients in either cohort required dose reduction or delay. At 12 weeks, no patients receiving cabozantinib 40 mg daily required dose reduction or interruption. One patient receiving cabozantinib 20 mg daily experienced a grade 3/4 adverse event within the first 6 weeks, but this patient had pre-existing anorexia and fatigue, which worsened to grade 3.⁹ Phase III trials are evaluating cabozantinib in postdocetaxel patients with metastatic CRPC and bone metastases.

The reduction in bone metastases is unusual in patients treated for metastatic CRPC, and the mechanism by which it occurs is not clear. Both MET and VEGFRs are expressed on osteoblasts and osteoclasts, and MET is frequently expressed in bone metastases and in poorly differentiated prostate cancers.¹⁰ Moreover, the MET and the VEGF pathways may interact via neuropilin.⁷

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

Orteronel (TAK-700) is a selective 17,20 lyase inhibitor that decreases androgenic steroid production. Based on promising phase I data in patients with metastatic CRPC, the open-label, multicenter study was expanded to include a phase II component with 4 additional cohorts. Updated data were presented by Agus (Abstract 98). Eligible patients had not received prior chemotherapy, had a baseline testosterone level of less than 50 ng/dL, and had PSA levels of at least 5 ng/mL. Cohort 1 patients received twice-daily doses of orteronel 300 mg (n=23). Cohort 2 patients received orteronel 400 mg plus prednisone 5 mg (n=24). Treatment in cohort 3 was 600 mg plus prednisone 5 mg (n=26). Treatment in cohort 4 (n=24) was orteronel 600 mg daily. At data cutoff, 62% of patients had withdrawn from the study, including 19% due to adverse events and 19% for progressive disease. The most common treatment-emergent adverse events were fatigue (77%), nausea (47%), constipation (39%), and diarrhea (35%). The most common adverse events of at least grade 3 were fatigue (12%), hypokalemia (8%), hyperglycemia (5%), and diarrhea (4%). At 12 weeks, the proportions of patients with a PSA decrease of at least 50% were 63%, 50%, 41%, and 60% in cohorts 1, 2, 3, and 4, respectively. Of the 51 patients available for RECIST evaluation, 10 patients had a partial response, including 5 confirmed responses; 22 patients had stable disease; and 15 patients had progressive disease. At 12 weeks, median testosterone and median dehydroepiandrosterone (DHEA) levels decreased from baseline in all groups. Mean circulating tumor cell numbers decreased from 16.6 per 7.5 mL of blood at baseline to 3.9 per 7.5 mL of blood at 12 weeks. At 24 weeks, 37 of 59 evaluable patients had a PSA decrease of at least 50%.

Dasatinib

Dasatinib is an oral multikinase inhibitor that includes Src among its targets. Src is highly expressed in advanced prostate cancer and is thought to have a role in cell proliferation, invasion, and metastasis (Figure 7). To provide a more accurate assessment of androgen receptor signaling, a transcription-based activity signature was developed from LNCaP prostate cancer cells.¹¹ The resulting transcription signatures were then applied to different prostate cancer cell lines and to prostate tumors in order to reveal changes in androgen receptor activity as a function of hormone therapy and tumor progression. In patients who received no treatment, the transcription signatures reflected a high probability of androgen receptor activity, whereas in patients who received neoadjuvant androgen ablation,

the transcriptional signature predicted a very low level of androgen receptor activity. Analysis of the largest available published set of metastatic prostate cancer specimens showed that median androgen receptor activity decreased with cancer progression. The analysis also suggested that Src activity, and sensitivity to dasatinib, is increased in tumors with low androgen receptor activity, both in localized prostate cancers and in metastatic CRPC samples. This approach is being tested in clinical trials examining treatment with antiandrogen or dasatinib based on molecular signatures from patient biopsies.

In a phase II trial of 47 chemotherapy-naïve men with metastatic CRPC and increasing PSA levels, patients were treated with dasatinib monotherapy (100 mg or 70 mg, twice daily).¹² Lack of progression was achieved in 43%

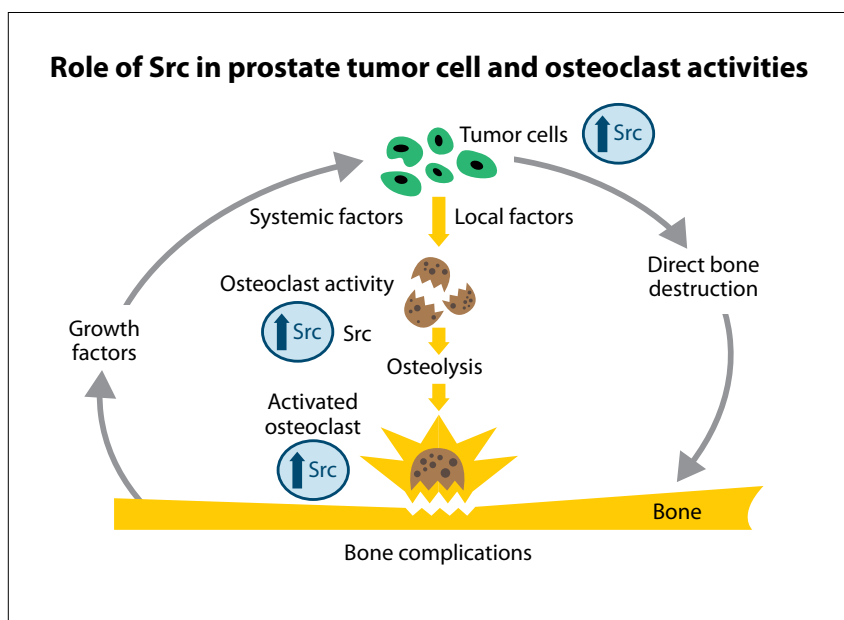


Figure 7. Src is highly expressed in advanced prostate cancer and is thought to have a role in cell proliferation, invasion, and metastasis. Adapted from Yu EY. General Session II. Castration-resistant prostate cancer—treatment sequencing and implementation: novel targets, agents, and trials. 2012 ASCO Genitourinary Cancers Symposium. San Francisco, CA: February 2-4, 2012.

ABSTRACT SUMMARY Neoadjuvant Sipuleucel-T in Patients With Localized Prostate Cancer: Immune Responses in Prostate Tumor Tissue

Fong presented results from an open-label phase II study (P07-1) conducted to elucidate the immunologic effects of sipuleucel-T prior to radical prostatectomy in patients with localized prostate cancer (Abstract 181). Starting 6–7 weeks prior to radical prostatectomy, patients received 3 infusions of sipuleucel-T at intervals of approximately every 2 weeks. Lymphocyte presence was determined by immunohistochemistry from biopsies of the prostate prior to treatment and tissue from the radical prostatectomy after treatment. The 42 enrolled patients had a median age of 61 years, and all had an ECOG performance status of 0. Thirty-eight patients (90%) received all 3 infusions of sipuleucel-T prior to radical prostatectomy. At the time of reporting, immunohistochemistry analysis had been completed for 19 patients. Based on operative complications, procedure time, and estimated blood loss, sipuleucel-T treatment did not appear to impact surgery. Treatment-related adverse events were reversible and manageable. Adverse events that occurred in greater than 10% of patients within 1 day of the infusion were fatigue, headache, and myalgia. In comparison to the pretreatment biopsies, significant increases of greater than 2-fold in the populations of CD3+ ($P=.0002$) and CD4+ ($P=.0002$) lymphocytes were observed at the tumor rim. In contrast, populations of CD8+ T cells or CD56+ cells were not significantly increased at the tumor rim compared to benign tissue. The investigators concluded that sipuleucel-T treatment may modulate the presence of lymphocytes at the prostate tumor site.

of patients at week 12 and in 19% of patients at week 24. Of 41 evaluable patients, 51% achieved a 40% or better reduction in urinary N-telopeptide by week 12, and 80% showed some level of reduction at any point in the study. Bone alkaline phosphatase was reduced at week 12 in 60% of the 40 evaluable patients, and 63% achieved some level of reduction while in the study. Dasatinib was generally well tolerated.

A phase I/II trial of docetaxel, prednisone, and dasatinib enrolled 46 patients with CRPC.¹³ Durable PSA reductions by 50% were observed in 57% of patients. Of 30 patients evaluable by RECIST, 60% had a partial response. In 30% of patients, a lesion disappeared via bone scan. Urinary N-telopeptide levels decreased in 87% of 38 patients, and bone-specific alkaline phosphatase levels decreased in 76% of 34 patients. Of 46 patients, 28% had a grade 3 or 4 toxicity.

Based on these results, the phase III READY (Randomized Study Comparing Docetaxel Plus Dasatinib to Docetaxel Plus Placebo in Castration-Resistant Prostate Cancer) trial was designed, randomizing 1,500 patients with metastatic CRPC and evidence of progression to docetaxel, prednisone, and placebo versus docetaxel, prednisone, and dasatinib.¹⁴ The primary endpoint is OS. This trial is ongoing, with results expected in 2013.

Custersin

Clusterin functions as a cytoprotective chaperone whose expression is increased in prostate tumors with higher Gleason scores and after androgen-deprivation therapy. It appears to have a role in apoptosis. Overexpression of clusterin confers resistance to hormone therapy, chemotherapy, and radiation. Custersin is an antisense oligonucleotide that is complementary to clusterin mRNA and has been shown to reduce clusterin expression in humans at 640 mg. Dose-dependent decreases in clusterin expression were observed in prostate cancer tumor samples and in lymph nodes of prostate cancer patients, based on

reverse-transcriptase polymerase chain reaction and immunohistochemistry.¹⁵

A phase II trial in men with metastatic CRPC randomized 82 patients to prednisone and docetaxel, with or without weekly custerisin (640 mg).¹⁶ The trial failed to demonstrate a difference between treatments in terms of PFS, the primary endpoint. However, exploratory survival analyses, although underpowered, suggested a clinical benefit in terms of reduced probability of death (HR, 0.50; 95% CI, 0.29–0.8; $P=.012$). These findings underpin the SYNERGY (Comparison of Docetaxel/Prednisone to Docetaxel/Prednisone in Combination With OGX-011 in Men With Prostate Cancer) trial, which will randomize 800 patients with metastatic CRPC to first-line docetaxel and prednisone with or without custerisin.¹⁷ The primary endpoint of the trial is OS. Secondary endpoints include PFS, PSA levels, patient reported outcomes, serum clusterin levels, and safety.

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ABSTRACT SUMMARY Overall Survival Benefit and Safety Profile of Radium-223 Chloride, a First-In-Class Alpha-Pharmaceutical: Results From a Phase III Randomized Trial (ALSYMPCA) in Patients With Castration-Resistant Prostate Cancer (CRPC) With Bone Metastases

Radium-223 chloride (Ra-223) is a first-in-class agent that targets bone metastases with high-energy alpha particles in a range of less than 100 microns. Parker presented results from the phase III, double-blind, international, randomized ALSYMPCA (Alpharadin [Radium-223] In Patients With Symptomatic Hormone-Refractory Prostate Cancer With Skeletal Metastases) trial, which compared Ra-223 plus best supportive care versus placebo plus best supportive care (Abstract 8). Eligible patients had progressive, symptomatic CRPC with at least 2 bone metastases based on scintigraphy and no known visceral metastases. Patients were receiving best supportive care and had previously received docetaxel, were ineligible for docetaxel, or had refused docetaxel. Patients were randomized 2:1 to receive 6 injections of Ra-223 (50 kBq/kg intravenously) every 4 weeks or matching placebo. Patients were stratified by prior docetaxel treatment, baseline alkaline phosphatase, and current bisphosphonate use. A planned interim analysis was conducted to assess OS. The study randomized 615 patients to Ra-223 and 307 patients to placebo from June 2008 through February 2011. Of 809 patients in the interim analysis data set—of whom 58% had received prior docetaxel—Ra-223 significantly improved median OS compared to placebo (14.0 months vs 11.2 months, respectively; HR, 0.695; 95% CI, 0.552–0.875; $P=.00185$). Ra-223 showed a favorable safety profile overall, and a 1.8% incidence of grade 3/4 neutropenia for Ra-223 (n=509) versus 0.8% with placebo (n=253). Thrombocytopenia was observed in 4% versus 2% of patients for Ra-223 versus placebo, respectively.

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Sipuleucel-T Product Characterization Across Different Disease States of Prostate Cancer

Antigen-presenting cell activation has correlated with OS in studies of sipuleucel-T.^{1,2} The randomized, controlled, phase III IMPACT trial showed a 4.1-month improvement in OS and a 22% reduction in the risk of death for patients treated with sipuleucel-T (HR, 0.78; 95% CI, 0.61–0.98; $P=.03$).¹ Data from the IMPACT trial and others have demonstrated that sipuleucel-T stimulates immune responses in patients with metastatic CRPC. To assess the immune response in different disease states, this study³ separately examined data from 4 phase III trials:

- NeoACT (Sipuleucel-T as Neoadjuvant Treatment in Prostate Cancer): an

open-label, phase II trial of sipuleucel-T as neoadjuvant treatment in men with localized prostate cancer.⁴

- IMPACT (Immunotherapy for Prostate Adenocarcinoma Treatment): a placebo-controlled, phase III trial in men with asymptomatic or minimally symptomatic metastatic CRPC.¹
- ProACT (To Evaluate Sipuleucel-T Manufactured With Different Concentrations of PA2024 Antigen): a phase II trial in men with asymptomatic or minimally symptomatic mCRPC.⁵
- OpenACT (Open-Label Active Cellular Immunotherapy): an open-label, phase II trial in men with metastatic CRPC.⁶

Patient peripheral blood mononuclear cells (PBMCs) were obtained from each subject by leukapheresis on weeks 0, 2, and 4. Sipuleucel-T was produced by culturing PBMCs in the presence of PA2024, a recombinant fusion protein encompassing prostatic acid phosphatase and granulocyte/macrophage colony-stimulating factor. Patients received 3 infusions of sipuleucel-T approximately every 2 weeks. Some patients in the NeoACT trial received a fourth “booster” infusion approximately 3 months after radical prostatectomy. In all studies, preculture and postculture cellular composition of samples was evaluated, as was CD54 antigen expression, an indicator of antigen-presenting cell activation. B-cell and T-cell activation was determined via flow cytometry. Cultures were examined specifically for mature B cells, activated mature B cells, memory B cells, regulatory T cells, and activated T cells.

Data from the 4 trials included 41 patients from NeoACT, 330 patients from IMPACT, 40 patients from ProACT, and 98 patients from OpenACT. Patient baseline demographics largely reflected the eligible disease state. Patients from NeoACT were younger and had a reduced disease burden relative to patients from the other trials. Although no patients from NeoACT had received prior chemotherapy (as specified by eligibility criteria), 19.1%, 27.5%, and 32.7% of patients from the IMPACT, ProACT, and OpenACT trials had received prior chemotherapy, respectively.

At weeks 0, 2, and 4, T cells (CD3+) generally represented a greater proportion of cells prior to culture in patients with an earlier disease state, relative to the proportion of antigen-presenting cells (C54+), B cells (CD19-), and natural killer cells (CD56+). No significant differences in cellular composition were observed in patient samples from the

ABSTRACT SUMMARY Parametric Effect Size Estimates From Sipuleucel-T Randomized Trials

In an analysis of data from the D9901 (*J Clin Oncol*. 2006;24:3089-3094) and IMPACT (*N Engl J Med*. 2010;363:411-422) trials, Blumenstein and colleagues showed that different statistical approaches can yield different estimates of the magnitude of the effect of treatment with sipuleucel-T (Abstract 75). Differences in median survival are frequently used to measure the size of treatment effect. However, other estimates can more fully represent the survival distributions, with a reduced likelihood of local variations. Nonparametric analysis of data from trials D9901 and IMPACT yielded median survival estimates of 4.1 months and 4.5 months, respectively. Semiparametric analyses of the HR, which was not stratified or adjusted, yielded estimates of 0.586 and 0.752 for the 2 trials, respectively. Blumenstein and colleagues used parametrical statistical models to provide alternative estimates of effect size. The models were based on the Weibull distribution and a modification of the Weibull distribution that allowed for delayed onset of treatment effect. For trial D9901, the estimate of median difference based on the Weibull model yielded a much larger effect compared to the nonparametric analysis (10.3 months [HR, 0.585] vs 4.5 months [HR, 0.586], respectively). The modified Weibull analysis, which yielded a median difference of 6.6 months (HR, 0.486), was also consistent with a greater effect. Weibull-based analysis of data from the IMPACT trial also showed an increased median difference compared to the nonparametric analysis (4.7 months vs 4.1 months). The HRs were similar for the original and the Weibull-based analyses (0.752 and 0.749 respectively). However, the delayed-effect, modified Weibull model did not support the theory of delayed effect for the IMPACT trial.

IMPACT and ProACT trials, both of which enrolled men with asymptomatic or minimally symptomatic metastatic CRPC. Upregulation of CD54+ cells was observed at weeks 2 and 4 in samples from all 4 trials. However, the increase in CD54 expression was most pronounced in PBMCs from NeoACT compared with samples from the other 3 trials ($P < .001$). Increases in CD54 expression of a similar magnitude were observed in PBMCs from IMPACT and ProACT.

B-Cell and T-Cell Responses

A comparison of samples from NeoACT and ProACT showed a greater proportion of naïve, mature B cells in both preculture and postculture samples, but the trend was not significant. However, the proportion of activated, mature B cells was higher in NeoACT samples at week 4 in preculture samples and at all time points in postculture samples ($P < .004$). No significant difference in the proportion of activated memory B cells was discerned between the 2 disease states represented by these 2 trials.

The proportion of the combined population of antigen-naïve and activated T cells remained relatively constant throughout treatment in early- and late-stage disease. Within the population of activated T cells, an antigen-specific T-cell immune response in both early- and late-stage disease was suggested by the increased expression of the early T-cell activation markers, CD134 and CD137. Immune priming in postculture PBMCs from NeoACT patients was suggested by a significant increase in the percent of CD4+ T cells ($P < .001$) and CD8+ T cells ($P \leq .0217$) expressing CD134+ and CD137+. ProACT samples showed a significant postculture increase of CD4+ CD134+ T cells ($P < .001$) and both CD134+ and CD137+ CD8+ T cells ($P \leq .0135$; Figure 8). A postculture increase in the proportion of CD4+ CD278+ T cells was observed for ProACT ($P = .0011$) but did not reach significance for

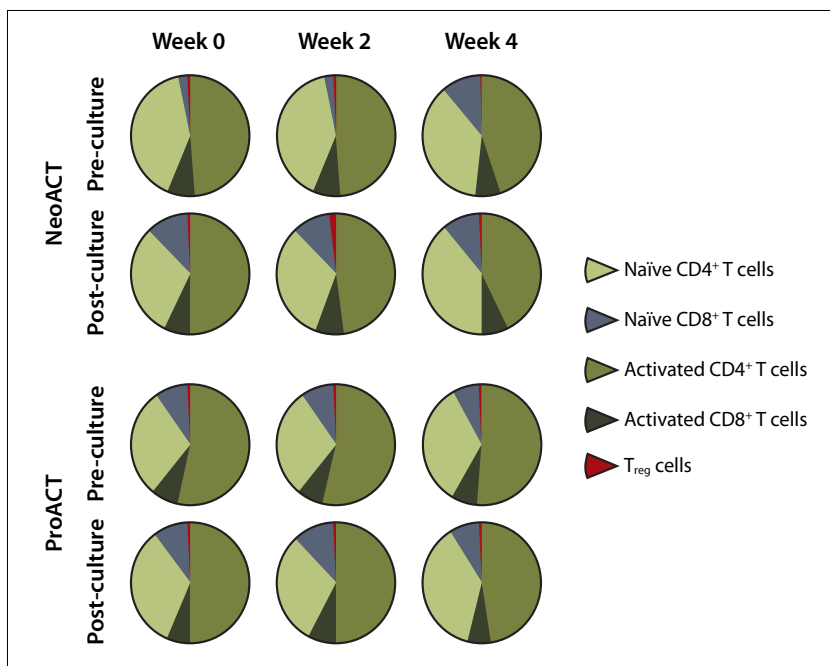


Figure 8. In a study evaluating cellular composition in patients receiving sipuleucel-T in clinical trials, the percentage of T_{reg} cells increased postculture in early-stage and late-stage disease. Adapted from Sheikh et al. *J Clin Oncol* (ASCO Genitourinary Cancers Symposium Abstracts). 2012;30(suppl 5): Abstract 142.

NeoACT ($P = .0640$). No significant increase in CD4+ CD279+ or CD8+ CD279+ cells was revealed for samples from either trial. The proportion of T regulatory cells in samples prior to culture did not change throughout treatment. Postculture samples from early ($P = .0205$) and late stage ($P < .001$) disease showed an increase in T regulatory cells in week 2; however, median values remained within normal limits (below 7%) for healthy individuals.

Cytokine Response Profiles

A low level of cytokine production was detected in week 0 culture supernatants from NeoACT and ProACT, but an increase was observed at week 2 relative to week 0 for NeoACT ($P < .001$) and ProACT ($P < .05$). A significant increase in cytokine production was also observed in week 4 compared with week 0 for NeoACT ($P \leq .0196$) and ProACT ($P < .05$). The increased levels of cytokines IL-2, IFN-gamma, IL-6, and IL-10 at weeks 2 and 4 rela-

tive to week 0 were consistent with the “prime-boost” phenomenon associated with immunization.

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Commentary

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The American Society of Clinical Oncology Genitourinary Cancers Symposium featured many important trials in men with advanced prostate cancer. Improvements in survival were demonstrated with the novel androgen receptor–targeted agent MDV3100 in men with castration-resistant prostate cancer who progressed after systemic chemotherapy. An alpha particle–emitting radioisotope, radium-223 chloride, also demonstrated improved survival in docetaxel-ineligible as well as docetaxel-refractory castration-resistant prostate cancer patients. Preliminary data were also presented with TAK-700 and OGX-427 in castration-resistant prostate cancer. Studies in sipuleucel-T further explored the agent's mechanism of action and assessed the improved responses seen in previous studies. A trial of denosumab aimed to correlate prostate-specific antigen (PSA) doubling times with bone metastases-free survival in men with nonmetastatic castration-resistant prostate cancer presenting with aggressive PSA kinetics.

Sipuleucel-T

The IMPACT (Immunotherapy for Prostate Adenocarcinoma Treatment) trial was a 512-patient, randomized study which compared sipuleucel-T to placebo in men with asymptomatic or minimally symptomatic castration-resistant prostate cancer.¹ Treatment consisted of 3 pheresis with subsequent reinfusion of the dendritic cell product raised against a prostatic acid phosphatase fusion protein. Patients who were randomized to the control arm had their pheresis product frozen and

stored. APC8015F is a dendritic cell preparation obtained from exposing the frozen cells to the same prostatic acid phosphatase fusion protein. After objective disease progression, patients in the control arm were offered 3 infusions of APC8015F. It is possible that the administration of this product influenced the survival data from the IMPACT study. Nahban et al used a rank-preserving structural failure time model to adjust survival for this potential confounding variable,² assuming that the treatment effect of APC8015F was equivalent to sipuleucel-T. Overall, 64% of the 171 control patients received APC8015F. Using the rank-preserving structural failure time model, the survival improved by a median of 7.8 months in favor of sipuleucel-T. The survival of those patients receiving APC8015F was 23.8 months versus 11.6 months for those patients who did not. Although these results are suggestive of an improved survival benefit, they must be interpreted with caution. Since physician choice of treatment played a role in whether a patient received APC8015F or other treatments, those who did not receive APC8015F may have had more favorable baseline characteristics.

Sheikh et al examined cellular composition, including CD54 upregulation, in subjects from 3 phase III trials examining sipuleucel-T.^{2,3-6} T-cell activation, B-cell activation, and cytokine production profiles were similar among the patients who were treated, and there was an increased CD54 upregulation after the second and third sipuleucel-T treatment consistent with a prime boost effect, which enhances immunological activation.

Another study led by Sheikh assessed the activation of immune agents in patients receiving sipuleucel-T who were treated neoadjuvantly.⁷ Activated T cells, interferon gamma, and IL-2 were upregulated after neoadjuvant sipuleucel-T. Memory cells, antigen-presenting cells, CD4+ T cells, and CD8+ T cells were all seen in this group of patients. No correlation could be made with clinical outcome in this group of patients, but these findings are another indicator that the immune system is activated with sipuleucel-T treatment.

In a similar trial, Fong et al examined immune responses in tissue among patients with localized prostate cancer who received neoadjuvant sipuleucel-T.⁸ They found an increased frequency of T cells at the rim between the benign and malignant glands. This finding implies that T cells may modulate lymphocytes at the tumor site, which suggests that the activated T cells target the primary tumor.

Denosumab

Bone metastases occur in nearly all men with fatal castration-resistant prostate cancer, and can result in significant pain. To date, there is no agent approved by the US Food and Drug Administration (FDA) which delays the onset of bone metastases in men with nonmetastatic castration-resistant prostate cancer. Denosumab, an inhibitor of RANK ligand, is currently approved for the prevention of skeletal-related events in men with castration-resistant disease. Smith et al randomized 1,432 men with nonmetastatic castration-resistant

prostate cancer and a PSA of more than 8 ng/mL or a PSA doubling time of more than 10 months to either denosumab or placebo.⁹ Overall, there was a 4.2-month delay in the development of metastatic disease in favor of denosumab. A subgroup analysis evaluated the treatment effect of denosumab in relationship to PSA doubling times; the shorter PSA doubling times appeared to have a greater treatment effect, with a median difference of 7.5 months for those patients with a PSA doubling time of less than 4 months.

Novel Agents

MDV3100 is an agent which prevents the translocation of the androgen receptor into the nucleus of the prostate cancer cell. In phase I studies, MDV3100 demonstrated activity in the predocetaxel and postdocetaxel settings, with PSA declines of more than 50% observed in 62% and 51% of patients, respectively. Scher et al presented results from the phase III AFFIRM (A Study Evaluating the Efficacy and Safety of Investigational Drug MDV3100 in Men with Advanced Prostate Cancer) trial, randomizing 1,199 patients who had been previously treated with docetaxel on a 2:1 basis to either MDV3100 or placebo.¹⁰ Patients were randomized to receive either MDV3100 or placebo. A median survival of 18.4 months was seen in the MDV3100-treated patients, a 4.8-month improvement in survival when compared to placebo. The MDV3100 arm had superior results in secondary outcome measures such as PSA declines of more than 50% from baseline (54.0% vs 1.5%), soft tissue response by RECIST (28.9% vs 3.8%), and time to PSA progression (8.3 vs 3.0 months). The distribution of toxicities observed in the MDV3100-treated patients was not significantly different than in those receiving placebo, except for 5 episodes of seizures in the MDV3100 arm. Three of these 5 patients had brain metastases, which

could have predisposed them to this toxicity. If approved by the FDA, MDV3100 will be used as second-line therapy, joining abiraterone and cabazitaxel in this clinical space. Biological markers clearly need to be developed to help determine which of these treatments should be used.

Parker et al provided overall survival and safety data from the phase III ALSYMPCA (Alpharadin in Symptomatic Prostate Cancer) trial, which examined radium-223 chloride in patients with castration-resistant prostate cancer.¹¹ The study population consisted of 2 different groups of patients: those who were not eligible to receive docetaxel and those who had received docetaxel. Radium-223 chloride plus best supportive care significantly improved median overall survival as compared with placebo plus best supportive care (14.0 months vs 11.2 months, respectively; $P=.00185$). These findings are in contrast to those in castration-resistant prostate cancer patients treated with strontium and samarium, who experienced improved pain control and time to pain progression without improved survival.

TAK-700 more selectively inhibits 17,20-lyase enzymatic activity than 17-hydroxylase activity. Unlike abiraterone, this selectivity affords it the ability to be administered without steroids, which are administered with abiraterone to prevent a compensatory rise in adrenocorticotrophic hormone (ACTH), and thus a mineralocorticoid excess. Agus et al updated a previous trial of 97 patients who received TAK-700, either with or without prednisone.^{12,13} Results demonstrated that TAK-700 at a dosage greater than 300 milligrams twice daily was active, and that it had similar activity with or without prednisone. The testosterone levels were more strongly correlated to outcome than dehydroepiandrosterone sulfate in this group of patients. TAK-700 is now in phase III trials, in which it is being administered either before or after docetaxel.

OGX-427 is an antisense compound targeted at heat shock protein (HSP) 27, a stress-activated protein expressed in a variety of different tumors. HSP-27 activity correlates with drug resistance, and thus down-regulation may lead to apoptosis and cell death. Chi et al presented the results of a randomized phase II trial of OGX-427 plus prednisone versus prednisone in chemotherapy-naïve men with castration-resistant prostate cancer.¹⁴ PSA declines of more than 50% (41% vs 20%) and objective soft tissue responses (38% vs 0%) were also superior in the OGX-427 arm. A similar effect was seen in patients who express circulating tumor cells, which portend a poorer survival if greater than 5 cells per 7.5 mL. In this study, 60% of patients randomized to the OGX-427 arm converted to less than 5 circulating tumor cells per 7.5 mL of blood, as compared with 20% in the prednisone-only arm.

Conclusions

As outlined in the presentation by Kantoff, using prior docetaxel therapy as a landmark for treatment (the predocetaxel vs postdocetaxel settings) may be an artificial designation that does not reflect a biologic difference.¹⁵ Without biological guidelines, it makes clinical sense to sequence these new agents from the least toxic to the most toxic. However, this may not reflect the most efficacious approach. Only biological studies using molecular markers and tumor imaging have the potential to sort out the sequence or combination of agents which will lead to the greatest improvement in survival.

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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 autologous peripheral blood mononuclear cells.

The most common adverse events, reported in patients in the PROVENGE group at a rate $\geq 15\%$, 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 $\geq 5\%$ 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 $\geq 5\%$ 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 $\geq 5\%$ 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 Incidence of Adverse Events Occurring in $\geq 5\%$ 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

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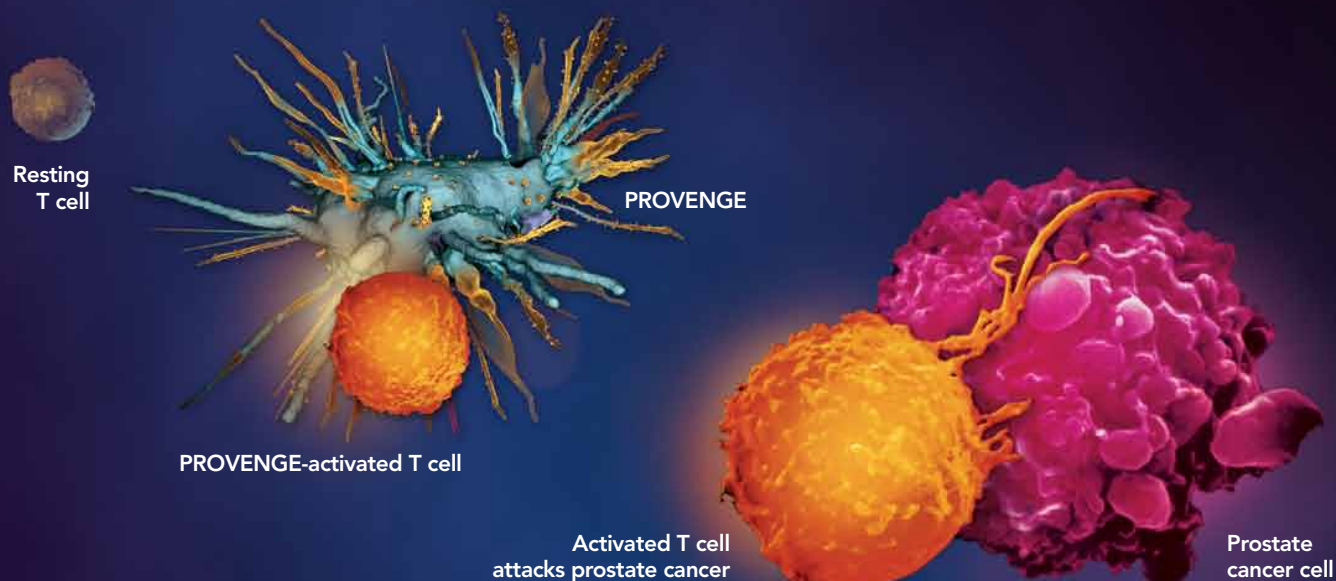
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PROVENGE
(sipuleucel-T)

IN ADVANCED PROSTATE CANCER...

PROVENGE

**ACTIVATE THE POWER OF THE IMMUNE SYSTEM.
EXTEND SURVIVAL.**



- **PROVENGE** extends median survival beyond 2 years¹
- Only 1.5% of patients treated with **PROVENGE** in the pivotal trial discontinued treatment due to adverse events²
 - The most common adverse events in **PROVENGE** trials were chills, fatigue, fever, back pain, nausea, joint ache, and headache²
- **PROVENGE** is the first and only FDA-approved immunotherapy for advanced prostate cancer
- The NCCN recommends **PROVENGE** as a *first-line* treatment for men with asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer (NCCN Category 1 recommendation)³

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 $\geq 15\%$) reported in the PROVENGE group were chills, fatigue, fever, back pain, nausea, joint ache, and headache.

For more information on PROVENGE, please see Brief Summary of Prescribing Information on adjacent page.

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PROVENGE®
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