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A SPECIAL MEETING REVIEW EDITION

Highlights in Advanced Prostate Cancer From the 2012 American Urological Association Annual Meeting and the 2012 American Society of Clinical Oncology Annual Meeting

Special Reporting on:

- Estimating the Overall Survival Benefit of Sipuleucel-T in the IMPACT Trial Accounting for Crossover Treatment in Control Subjects With Autologous Immunotherapy Generated From Cryopreserved Cells
- AFFIRM: Phase III Trial of the Androgen Receptor Signaling Inhibitor MDV3100
- What Will Happen if We Don't Screen for Prostate Cancer?
 A 10-Year Analysis of Metastatic Prostate Cancer as an Initial Presentation in an Underserved Population
- Overall Survival (OS) Benefit With Sipuleucel-T by Baseline PSA:
 An Exploratory Analysis From the Phase III IMPACT Trial
- Phase III Trials of Abiraterone Acetate in Patients With Chemotherapy-Naïve and Docetaxel-Pretreated MCRPC
- ALSYMPCA Trial: Phase III Trial of Radium-223 Chloride (Alpharadin) in Patients With CRPC With Bone Metastases

PLUS Meeting Abstract Summaries

With Expert Commentary by:

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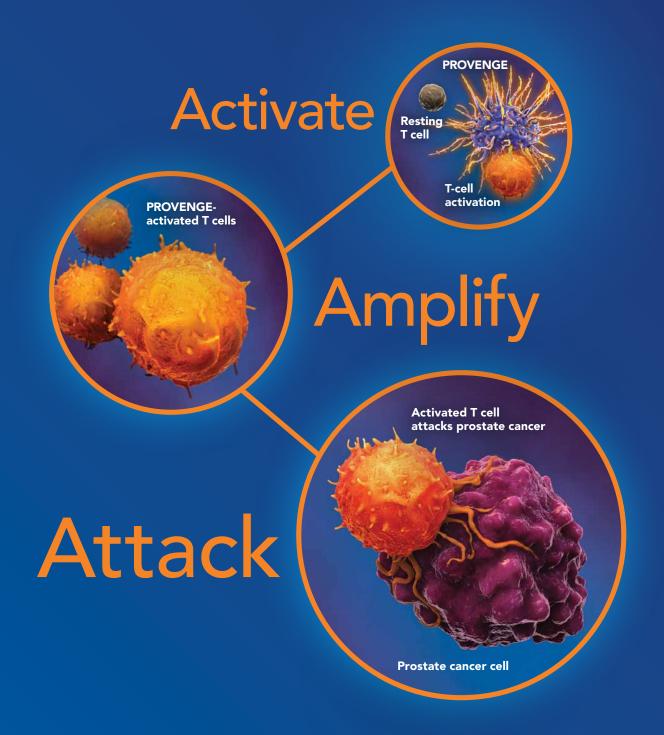
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In advanced prostate cancer

TREAT EARLY WITH PROVENGE TO



EXTEND SURVIVAL

PROVENGE activates the immune system to fight advanced prostate cancer

OVER

30%

Routinely scan to identify patients early

 Over 30% of men thought to have nonmetastatic castrate resistant prostate cancer (CRPC) were found to have metastatic disease when screened via imaging for a recent clinical trial¹

> 2 vears

PROVENGE extends median survival beyond 2 years²

• PROVENGE reduced the risk of death by 22.5% vs the control group (*P*=0.032)²

1.5%

PROVENGE provides a safety profile you can manage

- Only 1.5% of patients treated with PROVENGE in the pivotal trial discontinued treatment due to adverse events³
- The most common adverse events in PROVENGE trials were chills, fatique, fever, back pain, nausea, joint ache, and headache³

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 included 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.



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 ≥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 \leq 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 fatique (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 ≥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

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Estimating the Overall Survival Benefit of Sipuleucel-T in the IMPACT Trial Accounting for Crossover Treatment in Control Subjects With Autologous Immunotherapy Generated From Cryopreserved Cells

ipuleucel-T is an autologous cellular immunotherapy that is approved by the US Food and Drug Administration (FDA) for use in patients with asymptomatic or minimally symptomatic metastatic castrateresistant prostate cancer (mCRPC). The therapy is designed to stimulate antitumor activity by inducing an immune response against prostatic acid phosphatase (PAP), an antigen expressed in most prostate cancers.

Sipuleucel-T is manufactured by culturing freshly isolated peripheral blood mononuclear cells (PBMCs) with PA2024, a recombinant protein consisting of the PAP antigen linked with granulocyte-macrophage colony-stimulating factor (GM-CSF). PBMCs are obtained from each patient via leukapheresis performed on weeks 0, 2, and 4. PBMCs that have been cultured with PA2024 form the sipuleucel-T product, which is infused back into the patient over a total of 3 infusions administered approximately every 2 weeks.

The efficacy and safety of sipuleucel-T were evaluated in the randomized, phase III IMPACT (Immunotherapy for Prostate Adenocarcinoma Treatment) trial, which compared sipuleucel-T against a control treatment consisting of unstimulated PBMCs. Patients received infusions

of sipuleucel-T or control cells every 2 weeks for a total of 3 infusions. Upon disease progression, patients were treated at their physician's discretion. Patients in the control arm had the option of entering into an open-label phase II study evaluating a treatment based on the same protocol as sipuleucel-T, but using PBMCs that

were cryopreserved during the initial preparation of control cells.

The trial enrolled a total of 512 patients with asymptomatic or minimally symptomatic mCRPC; 341 patients were assigned to sipuleucel-T and 171 received the control treatment. As reported by Kantoff and colleagues in 2010, sipuleucel-T was

ABSTRACT SUMMARY Denosumab Delays Development of Multiple Bone Metastases in Men With Castration-Resistant Prostate Cancer

The effects of denosumab on parameters including the development of multiple bone metastases and symptomatic bone metastases were analyzed in a trial that enrolled 1,432 patients with non-mCRPC with a PSA of 8.0 ng/mL or higher within the past 3 months, and/or a PSA doubling time of 10 months or less (AUA Abstract 681). Patients were randomly assigned to receive denosumab, administered subcutaneously at 120 mg, or placebo, once every 4 weeks. The primary endpoint, bone metastasis-free survival, was defined as the time to first bone metastasis or death from any cause. Overall, 605 patients developed bone metastases during the treatment phase; in 59% of these cases, more than 1 bone metastasis was detected at the initial observation. Compared with placebo, denosumab was associated with a 24% reduction in the risk of developing multiple bone metastases (HR, 0.76; CI, 0.62-0.94; P=.011). The median time to multiple bone metastases was not reached in the denosumab group and was 40.8 months with placebo. Denosumab treatment was also associated with a 25% reduction in the risk of developing multiple or symptomatic bone metastases compared with placebo (HR, 0.75; 95% CI, 0.62-0.91; P=.004). The median time to multiple or symptomatic bone metastasis was 44.6 months and 37.0 months, respectively.

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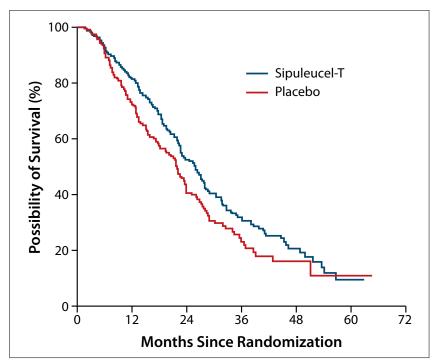


Figure 1. Kaplan-Meier estimate of overall survival in the IMPACT trial. Improvement is seen with sipuleucel-T compared with placebo. IMPACT=Immunotherapy for Prostate Adenocarcinoma Treatment. Adapted from Kantoff et al. *N Engl J Med.* 2010;363:411-422.

associated with a 22% reduction in the risk of death compared with the control treatment (median overall survival [OS], 25.8 vs 21.7 months; hazard ratio [HR], 0.78; *P*=.03; Figure 1).¹

An exploratory analysis of the IMPACT trial presented at the 2012 meeting of the American Urological Association (AUA) evaluated the effect of postprogression immunotherapy in the control group on survival outcomes.2 Overall, 109 patients (64%) opted to receive immunotherapy based on cryopreserved cells (called APC8015F) upon disease progression, whereas 36% did not. The median interval between disease progression and ACP8015F was 2.2 months (range, 0.5-14.6 months), and the median interval between randomization and ACP8015F was 5.2 months (1.8-33.1 months).

Among patients in the control group, median OS was longer in those who received APC8015F than in those

who did not, with a median OS of 23.8 months and 11.6 months, respectively. The median OS in the sipuleucel-T arm was 25.8 months.

An analysis of disease-related factors showed slightly more favorable prognosis among patients who received APC8015F than those who did not, as assessed by several factors, including prostate-specific antigen (PSA) level and Eastern Cooperative Oncology Group (ECOG) performance status (PS). However, the survival benefit observed with APC8015F remained after adjusting for baseline factors and postprogression factors.³

The investigators used a statistical model⁴ to reconstruct the control group survival as if no patients in the control group had received APC8015F. Using this method, the observed survival time post-APC8015F is reduced in patients who cross over. The model performs this analysis iteratively until the sipuleucel-T treatment effect converges.⁵

Using the statistical model, the median OS in the control group would decline from 21.7 months to 18.0 months if APC8015F is considered to be as effective as sipuleucel-T. This would indicate a 7.8-month median improvement in OS with sipuleucel-T over the control (HR, 0.60; 95% confidence interval [CI], 0.41-0.96). If the maximal effectiveness of APC8015F is considered to be 50% of that associated with sipuleucel-T, the median OS in the control group would be 20.7 months, indicating a 6.0-month difference with sipuleucel-T over the control (HR, 0.68; 95% CI, 0.49-0.97). If the maximal effectiveness of APC8015F is reduced to 0, sipuleucel-T would provide a 4.1-month improvement in median OS versus the control (HR, 0.77; 95% CI, 0.61-0.98). Based on this statistical model adjusting for the effect of APC8015F, the investigators concluded that the treatment effect of sipuleucel-T may be greater than previously reported.

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- 2. Gomella LG, Nabhan C, DeVries T, Whitmore JB, Frohlich M, George D. Estimating the overall survival benefit of sipuleucel-T in the IMPACT trial accounting for crossover treatment in control subjects with autologous immunotherapy generated from cryopreserved cells. Program and abstracts of the 2012 Annual Meeting of the American Urological Association; May 19-23, 2012; Atlanta, GA. Abstract 683.
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AFFIRM: Phase III Trial of Androgen Receptor Signaling Inhibitor MDV3100

nzalutamide (MDV3100) is an investigational agent designed to target signaling through the androgen receptor at multiple steps: it inhibits binding of androgens to the androgen receptor, inhibits nuclear translocation of the androgen receptor, and inhibits the association between the androgen receptor and DNA. No agonist effects have been observed in preclinical studies.

In a phase I/II study, enzalutamide demonstrated antitumor activity in patients with castrate-resistant prostate cancer (CRPC), regardless of whether they had received prior chemotherapy.1 At the 2012 American Society of Clinical Oncology (ASCO) meeting, De Bono and colleagues² presented results from the randomized, placebocontrolled, 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, which evaluated enzalutamide in patients with progressive CRPC with failure of docetaxel.

Between September 2009 and November 2010, 1,199 patients were recruited from 156 study centers in 15 countries on 5 continents. Patients were randomly assigned 2:1 to enzalutamide 160 mg daily (800 patients) or placebo (399 patients). Glucocorticoids were not required but were allowed, and were used in approximately 30% of patients in each arm. Patients with minor PSA changes could continue therapy.

Baseline characteristics were similar between groups; the median age was 69 years; 28% of patients had significant pain (pain inventory score ≥4), and 69–71% of patients had soft tissue disease. Approximately half of patients on each arm had received at least 3 prior lines of hormonal drug

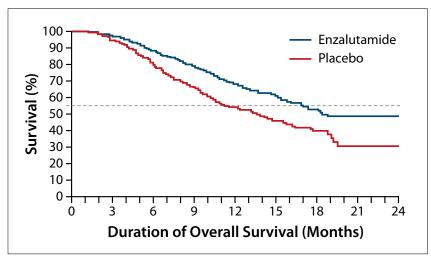


Figure 2. Overall survival in the AFFIRM trial. AFFIRM=Safety and Efficacy Study of MDV3100 in Patients With Castration-Resistant Prostate Cancer Who Have Been Previously Treated With Docetaxel-based Chemotherapy; CI=confidence interval; NYR=not yet reported. Data from De Bono JS et al. *J Clin Oncol* (ASCO Annual Meeting Abstracts) 2012;30(suppl): Abstract 4519^.

therapy, and approximately 24% had received 2 prior lines of chemotherapy.

After a median follow-up of 14 months, the median OS was significantly longer with enzalutamide versus placebo (18.4 vs 13.6 months; HR, 0.63; 95% CI, 0.53-0.75; P<.0001), representing a 37% reduction in the risk of death (Figure 2). Based on this significant and clinically meaningful improvement in OS, the independent data monitoring committee recommended halting and unblinding the trial and offering enzalutamide to patients in the placebo arm. The survival benefit was observed across all evaluated subgroups. Treatment is ongoing in 29% of patients in the enzalutamide arm.

Enzalutamide also demonstrated a high PSA response rate, with confirmed PSA reductions of at least 50% in 54% of patients and at least 90% in 25% of patients. Enzalutamide was significantly more effective than placebo in multiple secondary endpoints, including

median PSA-defined PFS (8.3 vs 3.0 months; HR, 0.25; *P*<.0001), RECIST ORR (29% vs 4%; *P*<.0001), median radiographic PFS (8.3 vs 2.9 months; HR, 0.40; *P*<.0001), median time to first skeletal-related event (16.7 vs 13.3 months; HR, 0.62; *P*<.0001), and quality-of-life response rate, as assessed by the Functional Assessment of Cancer Therapy-Prostate (FACT-P) (43% vs 18%; *P*<.0001).

The most common adverse event associated with enzalutamide was fatigue, reported in 34% of patients, versus 29% of patients receiving placebo. Seizures were reported in 0.6% of patients (5 cases) receiving enzalutamide versus no patients receiving placebo. Significant potential confounding factors were present in most cases.

Post-study anticancer therapy was common in both arms, and was reported in 41% of patients in the enzalutamide arm and 58% of patients in the placebo arm. Common postprotocol therapies included

abiraterone (21% and 24%, respectively), cabazitaxel (10% and 14%, respectively), docetaxel (9% and 14%, respectively), and mitoxantrone (3% and 11%, respectively).

In these patients with chemotherapy-pretreated mCRPC, enzalutamide extended survival by nearly 5 months, improved every secondary outcome measured, was well tolerated, and allowed once-daily oral treatment.

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What Will Happen if We Don't Screen for Prostate Cancer? A 10-Year Analysis of Metastatic Prostate Cancer as an Initial Presentation in an Underserved Population

creening for prostate cancer remains an important and controversial issue. The United States Preventive Services Task Force (USPSTF) recently recommended against PSA screening by PSA testing in healthy men, concluding that the current evidence is insufficient to assess the balance of benefit and harm of screening.1 However, other experts take issue with this stance, suggesting that the task force underestimated the benefits and overestimated the harms of prostate cancer screening. Therefore, the issue of prostate cancer screening remains hotly debated.

Results of an analysis evaluating the long-term consequences of detecting prostate cancer only at the time of metastatic disease were presented at the 2012 AUA meeting.2 The study focused on an underserved population of patients treated at an inner city municipal hospital. Patients of lower socioeconomic status, as well as individuals immigrating from developing nations, are less likely to seek medical attention and less likely to undergo cancer screening. Moreover, these individuals are not well represented in the randomized trials of PSA screening upon which the USPSTF recommendations are based.

The current study characterized the demographics, clinical features, and outcomes of individuals with metastatic prostate cancer as their initial presentation. The investigators identified their patient population using a prospectively maintained androgen deprivation therapy (ADT) database of an inner-city municipal hospital. A total of 148 individuals were identi-

fied who met the inclusion criteria and were diagnosed between 1999 and 2009. The median age of the patient group was 69 years; the median PSA was 154 ng/mL. Nearly all patients (99.9%) were African American. The median Gleason score was 8, and the

ABSTRACT SUMMARY Phase III Trial of Intermittent Vs Continuous Androgen Deprivation in Hormone-Sensitive Metastatic Prostate Cancer

S9346 was an international phase III trial of intermittent versus continuous androgen deprivation (ASCO Abstract 4). The trial was designed to determine the noninferiority of intermittent versus continuous androgen deprivation and to compare quality-of-life outcomes along with other secondary outcomes. The study enrolled patients with newly diagnosed metastatic prostate cancer and a PSA of 5 ng/mL or higher; prior neoadjuvant or adjuvant hormone therapy or finasteride was allowed with restrictions. Induction therapy consisted of goserelin plus bicalutamide for 7 months. Men with a normalizing PSA (≤4 ng/mL) at months 6 and 7 were randomly assigned to continuous (n=765) versus intermittent (n=770) androgen-deprivation therapy. The primary endpoint of the trial, overall survival, showed inferiority with intermittent versus continuous therapy, with a median OS of 5.1 years and 5.8 years, respectively, and 7-year OS rates of 38% and 42%, respectively. Subset analyses suggested a similar benefit with continuous versus intermittent therapy across patient groups aside from the group of patients with extensive disease, in whom there appeared to be a slight benefit with intermittent therapy. Among these patients, the median OS was 5.0 years with intermittent therapy and 4.4 years with continuous therapy, and 7-year OS rates were 33% in each arm. Conversely, among patients with minimal disease, the median OS was 5.2 years with intermittent therapy and 7.1 years with continuous therapy. The incidence of treatment-related adverse events was similar between arms, with no significant differences reported. No treatment-related deaths were noted.

median hematocrit was 39%. The median creatinine was 1.2 mg/dL, and 2 patients required dialysis. Visceral metastases were present in 19% of evaluated patients (14/75). Bone involvement was present in 97% of evaluated patients (143/148), with spinal cord compression in 7% of patients (11/148). Lymphadenopathy was present in 45% (50/111).

After a median follow-up of 3.5 years, the median time to hormonerefractory disease was 19 months, and the median cancer-specific survival was 4.2 years. The 2-year and 5-year cancerspecific survival rates were 68% and 39%, respectively.

The investigators concluded that, given the significant burden of metastatic prostate cancer for both patients and the economy, this group of men with undiagnosed aggressive metastatic prostate cancer must be diagnosed and treated. They suggested that this patient population has not been represented in randomized trials of prostate cancer screening, and a more thorough analysis would be nec-

essary to assess whether PSA screening would change the course of disease in these individuals.

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Overall Survival (OS) Benefit With Sipuleucel-T by Baseline PSA: An Exploratory Analysis From the Phase III IMPACT Trial

dentifying patient and disease characteristics associated with responses to certain treatments is important for guiding treatment selection for patients with mCRPC. A prespecified subgroup analysis of the IMPACT trial demonstrated that the survival benefit of sipuleucel-T was observed across all 47 reported subgroups, including patients with a high baseline PSA score, low hemoglobin, elevated serum lactate dehydrogenase (LDH), elevated serum alkaline phosphatase (ALP), higher ECOG PS, and a Gleason score of 8 or higher.¹

There appeared to be a trend toward a greater treatment effect of sipuleucel-T in patients whose baseline PSA fell below the median than in patients with a baseline PSA above the median, with hazard ratios of 0.685 and 0.865, respectively. This finding suggested that patients with earlier-stage disease may gain a greater relative benefit from sipuleucel-T than patients with more advanced disease.

To further evaluate the survival benefit with sipuleucel-T in different patient groups, Chodak and colleagues² conducted additional subset analyses; the results of these analyses were presented at the 2012 ASCO meeting. The investigators found a consistent OS benefit with sipuleucel-T across all patient groups evaluated;

however, there were several nonsignificant trends toward a greater benefit with sipuleucel-T in certain patient groups (Table 1). As previously noted, patients with a lower PSA appeared to

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

The NeoACT trial is examining immune activation resulting from administration of sipuleucel-T in the neoadjuvant setting (ASCO Abstract 2563). This open-label, phase II study is evaluating sipuleucel-T administered as neoadjuvant therapy in patients with localized prostate cancer. Patients received 3 infusions of sipuleucel-T approximately every 2 weeks, beginning 6-7 weeks prior to radical prostatectomy (RP). A subset of patients was randomly assigned to receive a sipuleucel-T booster infusion 12 weeks postsurgery or no booster. Patients are being followed for 72 weeks to monitor safety and immune responses. Of the 42 enrolled patients, 38 patients received all 3 pre-RP sipuleucel-T infusions, and 15 patients received a sipuleucel-T booster infusion post-RP. The investigators found that administration of sipuleucel-T in the neoadjuvant setting resulted in immune system activation consistent with that observed in other treatment settings, and included activation of antigen presenting cells (APCs), memory and activated mature B cells, CD4+T cells, and CD8+T cells. Immune activation was significantly enhanced from the first infusion to the third infusion, indicating a prime-boost phenomenon. Sipuleucel-T was associated with increased production of cytokines associated with immune activation, including TNF-alpha, IFN-gamma, and IL-2.

Table 1. Subset Analysis of Overall Survival in the IMPACT Trial

	Sipuleucel-T Median Overall Survival (Months)	Placebo Median Overall Survival (Months)	Sipuleucel-T Hazard Ratio (95% CI)	P Value, Test for Homogeneity of Treatment Effect
Baseline PSA, ng/mL				
≤50.1	32.6	23.8	0.685 (0.483-0.972)	0.331
>50.1	19.4	15.1	0.865 (0.632–1.183)	
Baseline LDH, U/L				
≤194	28.0	22.8	0.653 (0.467-0.912)	0.198
>194	22.0	17.3	0.887 (0.640–1.229)	
Baseline ALP, U/L				
≤103	30.5	25.1	0.825 (0.575–1.184)	0.798
>103	20.3	15.6	0.775 (0.569–1.055)	
Baseline Hgb, g/dL				
≤12.8	22.6	15.5	0.699 (0.511–0.955)	0.326
>12.8	27.3	27.8	0.886 (0.623–1.260)	
ECOG PS				
0	26.7	26.6	0.765 (0.589-0.994)	0.733
1	17.5	13.0	0.846 (0.507–1.409)	
Gleason score				
≤7	26.3	22.1	0.774 (0.593–1.010)	0.920
≥8	22.0	21.5	0.797 (0.489–1.299)	

ALP=alkaline phosphatase; CI=confidence interval; ECOG PS=Eastern Cooperative Oncology Group Performance Score; Hgb= hemoglobin; IMPACT=Immunotherapy for Prostate Adenocarcinoma Treatment; LDH=lactate dehydrogenase; PSA=prostate-specific antigen. Data from Chodak G et al. *J Clin Oncol* (ASCO Annual Meeting Abstracts) 2012;30(suppl): Abstract 4648.

gain more benefit from sipuleucel-T, as did patients with a baseline LDH at or less than 194 U/L versus greater than 194 U/L (HR, 0.653 vs 0.887), baseline hemoglobin level at or less than 12.8 g/dL versus greater than 12.8 g/dL (HR, 0.699 vs 0.886), and ECOG PS of 0 versus 1 (HR, 0.774 vs 0.846).

Gleason score appeared to have a minimal effect on the benefit of sipuleucel-T, with OS hazard ratios similar in patients with a baseline Gleason score of 7 or less versus 8 or higher (0.774 vs 0.797). Moreover, in the overall population, the benefit of sipuleucel-T did not vary greatly according to ALP level, with hazard ratios of 0.825 and 0.775 with baseline ALP levels at or less than 103 U/L and higher than 103 U/L, respectively. However, among the 247 patients with metastatic disease in the bone only, the treatment effect was greater in patients with a higher baseline ALP than in those with a lower ALP, with hazard ratios of 0.592 and 0.776, respectively.

ABSTRACT SUMMARY Correlation of Increased Eosinophil Count Following Sipuleucel-T Treatment With Outcome in Patients (Pts) With Metastatic Castrate-Resistant Prostate Cancer (MCRPC)

In the randomized, phase III IMPACT trial, sipuleucel-T was associated with transient increases in the concentration of eosinophils. An analysis presented at ASCO 2012 assessed changes in eosinophil counts in sipuleucel-T-treated patients correlated with clinical outcomes or immune responses (ASCO Abstract 4650). The investigators pooled data from 3 phase III trials (D9901, D9902A, and IMPACT). Of 377 evaluable sipuleucel-T-treated patients, 27.9% of patients had eosinophilia—defined as an eosinophil count above the upper limit of normal for patients with a normal baseline level, or a maximum change from baseline within the top quartile—at any time in weeks 2-16 of treatment. The investigators noted a significant association between eosinophilia and several prognostic factors, including Halabi score (P=.007), baseline PSA (P=.033), and hemoglobin level (P<.001), in addition to prior docetaxel treatment (P=.012). In an unadjusted analysis, eosinophilia was associated with a trend toward longer OS (HR, 0.75; 95% CI, 0.56-1.01; P=.057) and a significant improvement in prostate cancer-specific survival (HR, 0.71; 95% CI, 0.53–0.97; P=.031). Higher degrees of eosinophilia were associated with greater increases in antigen-specific humoral responses at weeks 6, 14, and 26, and enhanced production of Th2-type cytokines, including IL-2, IL-5, and TARC. Individuals with eosinophilia were more likely to develop infusion-related symptoms such as pyrexia and nausea. However, no patients developed hypereosinophilic syndrome.

ABSTRACT SUMMARY Comparing the Ability of Clinicians and a Nomogram Model at Predicting Future 99mTc-Bone Scan (BS) Positivity in Patients (pts) With Rising Prostate-Specific Antigen (PSA) Following Radical Prostatectomy (RP) for Prostate Cancer (PCa)

The availability of new therapies for patients with mCRPC has made the identification of asymptomatic metastases an increasingly essential task in order to guide clinical decision-making. The accuracy of a nomogram model was compared with the accuracy of a group of 24 prostate cancer experts for predicting future metastases in patients with prostate cancer who had not received antigen-deprivation therapy and had a rising PSA level following radical prostatectomy (RP) (ASCO Abstract 4652). The Slovin nomogram accounted for baseline PSA, PSA doubling time, T-stage, Gleason score, 1-year PFS, 2-year PFS, and median PFS. The experts included 24 clinicians, including urologists and oncologists. The experts reviewed the charts of 25 androgen-deprivation therapy-naïve patients post-RP with biochemical recurrence who had received treatment at the Cleveland Clinic. The cohort included 8 patients with a positive bone scan within a year of biochemical recurrence and 17 randomly selected patients who did not have a positive bone scan for at least 1 year of biochemical recurrence. All patients were white, with a median age of 62 years; the median PSA at biochemical recurrence was 1.2 ng/mL, and the PSA doubling time ranged from 1.3 months to 11.7 months. For each patient, clinicians were asked to predict the likelihood of a positive bone scan in 1 year. Overall, the nomogram consistently provided a more accurate prediction than the clinicians. There was substantial variation between the clinicians' predictions for each patient. None of the experts outperformed the nomogram, although the urologists' predictions were significantly more accurate than those of the oncologists. In general, clinicians tended to overestimate the risk of M1 disease.

Of the 6 evaluable characteristics included in a prognostic model³ in hormone-refractory metastatic prostate cancer—LDH, PSA, alkaline phosphatase, Gleason score, ECOG PS, and hemoglobin—none showed a statistically significant interaction with the treatment. Moreover, all of these factors except Gleason score were

significant independent predictors of survival in a multivariate analysis.

Based on the initial preplanned subset analysis, which showed a greater benefit with sipuleucel-T in patients with a baseline PSA below versus above the median, the investigators conducted an exploratory analysis further evaluating the benefit

of sipuleucel-T according to baseline PSA quartile. The analysis revealed an association between increasing baseline PSA quartile and reductions in multiple other prognostic features, including median LDH, median ALP, median hemoglobin, ECOG PS, and Gleason score. Patients with a higher PSA were also more likely to have previously received docetaxel.

The investigators found that the greatest survival benefit of sipuleucel-T was attained in patients with the lowest baseline PSA levels. Among patients in the lowest PSA quartile (<22 ng/mL), the median OS was 41.3 months with sipuleucel-T and 28.3 months with the control treatment, a difference of 13.0 months (HR, 0.51; 95% CI, 0.31–0.85). Conversely, among patients in the highest PSA quartile (>134.1 ng/mL), the median OS with sipuleucel-T and control were 18.4 months and 15.6 months, respectively, for a difference of 2.8 months (HR, 0.84; 95% CI, 0.55-1.29). The researchers concluded that these findings support the use of sipuleucel-T as early as possible in mCRPC.

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Phase III Trials of Abiraterone Acetate in Patients With Chemotherapy-Naïve and Docetaxel-Pretreated MCRPC

The recently approved androgen biosynthesis inhibitor abiraterone acetate (AA) was the subject of several presentations at the 2012 ASCO meeting. Abiraterone acetate (AA) is a selective, orally available inhibitor that blocks CYP17 activity, resulting in inhibition of androgen synthesis both in adrenal glands and in the tumor.1 AA was FDA-approved in 2011 for use in combination with prednisone for the treatment of patients with mCRPC who have received prior chemotherapy containing docetaxel. This approval was based on results of the phase III trial COU-AA-301, which compared AA plus prednisone versus placebo plus prednisone in patients with CRPC previously treated with docetaxel. At the 2012 ASCO meeting, Goodman and colleagues presented an updated survival analysis from the trial based on patients' docetaxel treatment history.²

Also presented at ASCO 2012 was a late-breaking abstract with results of an interim analysis of the second phase III trial, COU-AA-302, which evaluated the efficacy and safety of AA in chemotherapy-naïve patients with mCRPC.³ Both trials were multinational, randomized, double-blind, placebo-controlled studies in which patients were randomly assigned to AA (1,000 mg daily) with prednisone (5 mg twice daily) or placebo plus prednisone (5 mg twice daily). Prednisone is administered with AA to minimize toxicity.

In his presentation of the COU-AA-302 data, Charles Ryan, MD, explained that progression of mCRPC can occur over a 2-4-year period and is marked by characteristic events, including PSA progression, tumor/bone progression, pain, ECOG PS decline, and death.³ Based on the potentially long interval between PSA progression and eventual death, the investigators selected 2 co-pri-

ABSTRACT SUMMARY Neoadjuvant Sipuleucel-T in Localized Prostate Cancer: Effects on Immune Cells Within the Prostate Tumor Microenvironment

Data from the NeoACT study were analyzed to determine the immunologic effects of neoadjuvant sipuleucel-T on the prostate tumor microenvironment (ASCO Abstract 2564). Although sipuleucel-T is thought to induce an immune response against tumor cells, studies of sipuleucel-T in patients with mCRPC have focused on the immune response in peripheral blood rather than in the tumor site. The ability of sipuleucel-T to induce infiltration of tumor-specific cells into the tumor has not been directly evaluated. This study used immunohistochemical analysis to assess immune cell infiltration into the tumor following sipuleucel-T treatment in the NeoACT study. Compared with pretreatment biopsy samples, RP-obtained post-treatment samples were associated with an increase in the frequency of total (CD3+) T cells, T-helper cells (CD3+/CD4+), cytotoxic T cells (CD3+/CD8+), and regulatory T cells (CD3+/CD4+/FoxP3+) in the prostate. T cells were localized at the tumor interface between healthy and malignant tissue. The investigators concluded that sipuleucel-T modulates the frequency of lymphocytes in prostate cancer tissue.

mary endpoints for COU-AA-302: radiographic progression-free survival (rPFS), rigorously defined and centrally assessed, and OS.

The trial enrolled asymptomatic, or minimally symptomatic, patients with progressive, chemotherapy-naïve mCRPC. A total of 1,088 patients were randomly assigned to AA plus prednisone (546 patients) or placebo plus prednisone (542 patients). Patients were stratified by ECOG PS (0 vs 1). The treatment arms were well balanced in regard to demographic, clinical, and prognostic variables. The median age was approximately 70 years.

After a median follow-up of 22 months, AA plus prednisone was significantly more effective than placebo plus prednisone as assessed by both median OS (not reached vs 27.2 months; HR, 0.75; 95% CI, 0.61–0.93; *P*=.0097) and median rPFS (not reached vs 8.3 months; HR, 0.43; 95% CI, 0.35–0.52; *P*<.0001; Figure 3) In subgroup analyses, the efficacy benefit

of AA appeared similar across patient subgroups for both OS and rPFS.

AA plus prednisone was also significantly more effective than placebo plus prednisone as assessed by the proportion of patients attaining a PSA decline of at least 50% (62% vs 24%; *P*<.0001), the objective response rate (ORR; 36% vs 16%; risk ratio, 2.27; *P*<.0001), and other secondary endpoints, including time to opiate use, chemotherapy, ECOG PS deterioration, and PSA progression.

The most common adverse event in both arms was fatigue, occurring in 39% of patients receiving AA plus prednisone and 34% of patients receiving placebo plus prednisone. Compared with placebo plus prednisone, AA plus prednisone was associated with higher rates of ALT and AST increases (12% vs 5% and 11% vs 5%, respectively) and cardiac disorders (19% vs 16%). Liver function test abnormalities typically developed in the first few months of treatment. The

ABSTRACT SUMMARY Design of a Phase II Randomized, Open-Label Trial of DN24-02, an Autologous Cellular Immunotherapy Targeting HER2/neu, in Patients With Surgically Resected Urothelial Cancer at High Risk of Recurrence

An investigational immunotherapeutic strategy targeting HER2/neu is currently being evaluated in a phase II trial (ASCO Abstract TPS4673). DN24-02 is an autologous cellular immunotherapy product that is manufactured by culturing isolated autologous PBMCs with a recombinant antigen containing components of HER2/neu linked to GM-CSF to enhance activation of APCs. The study plans to enroll 180 patients with urothelial cancer who have undergone radical resection, including lymph node dissection, within 12 weeks and who have no evidence of residual disease. HER2/neu tissue expression of 1+ or higher by immunohistochemistry is required, and any prior neoadjuvant chemotherapy had to have been administered at least 60 days prior to registration. All patients must have high-risk disease, defined as pathologic tumor stage at or above pT2, positive lymph node (N+) status for patients who have received neoadjuvant therapy and pathologic stage at or above pT3, or positive lymph node (N+) status for patients who have not received neoadjuvant chemotherapy. Patients in the DN24-02 arm will undergo leukapheresis at weeks 0, 2, and 4 to obtain PBMCs for DN24-02 production. They will receive 3 infusions of DN24-02, each approximately 2-3 days after leukapheresis. The primary endpoint of the study is overall survival. Secondary endpoints include safety, disease-free survival, immune response, and magnitude of CD54 upregulation after DN24-02 administration.

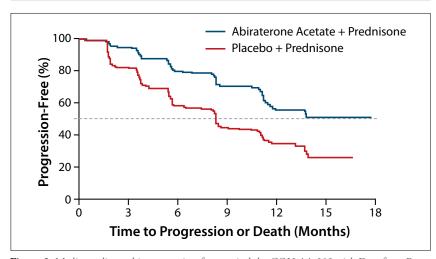


Figure 3. Median radiographic progression-free survival the COU-AA-302 trial. Data from Ryan CJ et al. *J Clin Oncol* (ASCO Annual Meeting Abstracts) 2012;30(suppl): Abstract LBA4518.

investigators noted that no new safety concerns have been identified with the extended treatment in this trial.

At the time of the interim analysis, treatment had been discontinued in 69% of patients receiving AA and 84% of patients receiving placebo. The most

common reasons for discontinuation were radiographic clinical progression (21% in the AA arm and 30% in the placebo arm) and unequivocal clinical progression (21% in the AA arm and 25% in the placebo arm)—defined as pain requiring opiates, chemotherapy,

palliative radiotherapy, decline in ECOG PS, or surgical intervention.

Subsequent therapy was administered to 44% of patients in the AA arm and 60% of patients in the control arm. The most frequently used subsequent therapy was docetaxel, administered to 38% of patients in the AA arm and 53% of patients in the placebo arm. AA was used as subsequent therapy in 10% of patients in the placebo arm and 5% of patients in the AA arm. Based on the efficacy outcomes in the second interim analysis, the study was unblinded in February 2012, and patients in the control arm were offered the study treatment. The investigators concluded that AA plus prednisone delayed disease progression, extended survival, and delayed pain and ECOC PS decline.

Also presented at ASCO 2012 was an analysis from COU-AA-301, the registrational trial of AA in patients with mCRPC with progressive disease after docetaxel. Patients had received a luteinizing hormone-releasing hormone analog or surgical castration and at least 1 course of docetaxel. Patients could have failed 1 or 2 chemotherapy regimens. A testosterone level higher than 50 ng/dL was required, as was an ECOG PS of 0-2. Enrollment took place between May 2008 and July 2009 at 147 study sites in 13 countries. A total of 1,195 patients were randomly assigned 2:1 to AA plus prednisone (797 patients) or placebo plus prednisone (398 patients).

Baseline characteristics in the COU-AA-301 study were well-balanced between the arms: the median age was 69 years, 45% of patients had significant pain present at baseline, 30% of patients had received 2 prior chemotherapy regimens, and nearly 70% of patients had radiographic progression at baseline. Metastatic disease was detected in the bone in 90% of patients. Metastatic disease in the visceral organs was found in 29% of patients assigned to AA and in 24% of patients assigned to placebo.

ABSTRACT SUMMARY Development of a Nomogram Model Using a Very Large Sample of Patients (pts) to Predict the Risk of 99mTc-Bone Scan (BS) Positivity in Pts Receiving Androgen Deprivation Therapy (ADT) for Prostate Cancer (PCa)

A nomogram model is in development to predict the risk of bone scan positivity in patients with prostate cancer receiving ADT (ASCO Abstract 4552). The investigators developed the model based on a retrospective record review of patients receiving treatment for prostate cancer at the Memorial Sloan-Kettering Cancer Center between 2000 and 2011. Of the 3,988 bone scan records analyzed, 968 tested positive. Patients had an average of 1.9 prior negative scans before the positive scan result. Of the 13 parameters investigated, there were 9 variables that were found to have a potential effect on current bone scan positivity: PSA, PSA doubling time, number of previous negative bone scans, year of bone scan, most recent Gleason grade sum, prostatectomy, radiotherapy, chemotherapy, and estrogen therapy. These 9 variables were all included in the nomogram, although year of bone scan lost significance after controlling for other factors. The resulting nomograph yielded high predictive accuracy, with a C-index of 0.748. The investigators concluded that nomograms should be incorporated in clinical practice to aid treatment decisions.

After a median follow-up of 12.8 months, AA plus prednisone was associated with a significant improvement in OS versus placebo plus prednisone, with a median OS of 14.8 months and 10.9 months, respectively (HR, 0.54; 95% CI, 0.54–0.77; *P*<.001).⁴ This benefit remained in an updated survival analysis conducted after 775 deaths, with a median OS of 15.8 months and 11.2 months, respectively (HR, 0.74; 95% CI, 0.64–0.86; *P*<.0001).⁵

At the 2012 ASCO meeting, Goodman and colleagues presented results of an analysis evaluating the effect of various docetaxel treatment variables on the survival benefit of AA.² The investigators noted that the history of docetaxel use was also similar between arms; docetaxel was administered as the first chemotherapy in 20% of patients and as a single agent in 66% of patients. The most common reasons for docetaxel discontinuation were progressive disease (45%), completion of planned therapy (37%), and toxicity (12%). Approximately 29% of patients

received their first dose of study drug (AA or placebo) within 3 months of their last dose of docetaxel. The median duration of docetaxel exposure was 5.3 months in the AA arm and 5.0 months in the placebo arm.

The median survival duration was significantly longer with AA versus placebo as measured from the first dose of prior docetaxel (32.6 vs 27.6 months; HR, 0.75; 95% CI, 0.65–0.88; P=.0002) and as measured from the last dose of prior docetaxel (23.2 vs 19.4 months; HR, 0.74; 95% CI, 0.64–0.86; P<0001).

The significant survival benefit of AA versus placebo was observed regardless of the reason for discontinuation of prior docetaxel. However, among the patients assigned to the AA arm, median OS was significantly shorter in patients who discontinued docetaxel due to progressive disease than in those who discontinued due to any other reason (14.2 vs 17.0 months; HR, 0.77; 95% CI, 0.64–0.92; *P*=.0041).

The survival benefit of AA versus placebo was observed both in patients who had started AA within 3 months of prior docetaxel (median OS, 15.0 months vs 10.7 months; HR, 0.62; 95% CI, 0.47–0.83; *P*=.0009) and in patients with a longer interval between therapies (median OS, 16.1 months vs 11.8 months; HR, 0.77; 95% CI, 0.64–0.92; *P*=.0036).

The improvement in OS with AA versus placebo was also observed regardless of the duration of prior docetaxel, although the difference did not reach statistical significance among patients with a docetaxel treatment duration of 3 months or less (likely due to a small sample size). Overall, the survival benefit of AA over placebo was maintained regardless of the timing and duration of prior docetaxel and the reason for docetaxel discontinuation. However, there was less benefit among patients who discontinued docetaxel due to progressive disease than for other reasons.

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ALSYMPCA Trial: Phase III Trial of Radium-223 Chloride (Alpharadin) in Patients With CRPC With Bone Metastases

Bone metastases affect more than 90% of patients with mCRPC, resulting in an increased risk of morbidity and mortality. Patients with bone metastases are at risk of multiple skeletal-related events, including spinal cord compression, pathologic fractures, requirements for surgery, and external beam radiation therapy. More effective treatments are needed to target bone disease in mCRPC.

One investigational strategy being evaluated for the treatment of bone metastases is the alpha-emitter radium-223. Radium is a calcium mimic, naturally targeting new bone growth surrounding bone metastases. Radium-223 thus targets bone metastases and emits high-energy alpha particles that act in a short diameter, allowing the potent, targeted delivery of radiation therapy to adjacent tumor

cells. In patients with osteoblastic lesions, radium-223 binds to newly laid bone, in particular to the calciumenriched portion of the bone. Alpha particles are delivered to adjacent tumor cells, inducing the formation of double-strand DNA breaks.

The efficacy and safety of radium-223 was evaluated in the randomized, phase III ALSYMPCA (Alpharadin in Symptomatic Prostate Cancer) trial, which enrolled patients with confirmed, symptomatic CRPC with at least 2 bone metastases and no visceral metastases. Patients had either previously received docetaxel or were considered unfit for docetaxel.

A total of 921 patients were randomly assigned 2:1 to receive radium-223 (50 kBq/kg), administered every 4 weeks for 6 total injections or placebo. All patients also received the best standard

of care, which included almost anything except chemotherapy. Nearly all patients also received secondary hormonal manipulations. Patients were stratified by total ALP (<200 U/L vs ≥220 U/L), bisphosphonate use (yes vs no), and prior docetaxel use (yes vs no).

The 2 arms were generally well balanced in regard to age, race, extent of disease, pain index, and baseline laboratory parameters. Approximately 56% of patients had significant cancer pain, with a cancer pain index of 2 or higher, and 41% of patients had more than 20 metastases detected.

At the 2012 AUA meeting, Oliver Sartor, MD, presented outcomes from a preplanned interim efficacy analysis after 320 events from the first 809 patients randomized.³ At that time, radium-223 demonstrated a significant OS benefit over placebo, with a median OS of 14.0 months and 11.2 months, respectively (HR, 0.70; 95% CI, 0.55–0.88; *P*=.0019). Based on this survival advantage, the trial was stopped early and the data safety monitoring committee recommended allowing crossover for patients on the control arm.

An updated analysis of the ALSYMPCA trial was presented several weeks later at the 2012 ASCO meeting by Chris Parker, MD, who reported outcomes after 528 OS events from all 921 randomized patients.⁴ This updated analysis, which was completed before patients in the placebo arm had crossed over and after patients in the experimental arm had completed therapy, confirmed the survival benefit of radium-223. Median OS was 14.9 months with radium-223 and 11.3 months with placebo (HR, 0.70; 95% CI, 0.58–0.83; *P*=.00007; Figure 4).

Subgroup analyses showed a similar benefit with radium-223 across patient groups, although patients with a serum ALP below 220 U/L appeared

ABSTRACT SUMMARY Final Analysis of Intergroup Randomized Phase III Study of Androgen Deprivation Therapy (ADT) Plus Radiation Therapy (RT) in Locally Advanced Prostate Cancer (CaP) (NCIC-CTG, SWOG, MRC-UK, INT: T94-0110)

Final data were presented for an intergroup, randomized, phase III trial evaluating the role of radiotherapy added to continuous ADT in men with locally advanced prostate cancer, which was defined as T3/T4 N0/Nx disease, T2 disease with a PSA higher than 40 $\mu g/L$, or T2 disease with a PSA higher than 20 $\mu g/L$ and a Gleason score of 8–10 (ASCO Abstract 4509). A total of 1,205 patients were randomly assigned to ADT plus radiotherapy (n=603) or ADT alone (n=602). ADT consisted of bilateral orchiectomy or a LHRH agonist (with 2 weeks' antiandrogen therapy and an option to continue). Radiotherapy was administered at a total dose of 65-69 Gy to the prostate and the pelvis (n=420) or to the prostate alone (n=166). In an interim analysis, ADT plus radiotherapy was significantly more effective than ADT alone, as assessed by both 7-year OS rate and 7-year disease-specific survival. These findings were confirmed in this final analysis, after a median follow-up of 8 years. At that time, 10-year OS rates with ADT plus radiotherapy and ADT alone were 55% and 49%, respectively, and the cumulative incidence of prostate cancer-related deaths were 15% and 26%, respectively, at 10 years. Radiotherapy was associated with transient bowel and urinary quality-of-life impairments over ADT alone, although these differences were no longer detectable at 36 months.

ABSTRACT SUMMARY SWOG S0421: Phase III Study of Docetaxel (D) and Atrasentan (A) Versus Docetaxel and Placebo (P) for Men With Advanced Castrate Resistant Prostate Cancer (CRPC)

SWOG S0421 is a randomized, double-blind, phase III trial comparing docetaxel plus atrasentan versus docetaxel plus placebo in patients with progressive mCRPC with bone metastases (ASCO Abstract 4511). Patients were randomly assigned to docetaxel 75 mg/m² every 3 weeks and prednisone 10 mg plus either oral atrasentan 10 mg daily (n=492) or placebo daily (n=485). Patients were stratified by type of progression, pain level, presence of extraskeletal disease, and bisphosphonate use. Study treatment was continued until disease progression. There was no difference in outcomes with docetaxel plus atrasentan and docetaxel plus placebo, with a median PFS of 9 months in each arm (2-year PFS rate 16%) and a median OS of 18 months (2-year OS rate, 37–38%). RECIST confirmed response rates were 13–14%, and the confirmed PSA response rate was 49% in each arm. A safety analysis revealed no significant adverse events associated with atrasentan. Notably, the incidence of docetaxel-associated grade 4 or higher lung toxicity was lower in the atrasentan arm than in the control arm, affecting 2 patients in the atrasentan arm (with 0 deaths) and 13 patients in the control arm (with 3 deaths). Although efficacy outcomes were equivalent in the overall patient population, correlative studies have identified bone metabolism biomarkers that are associated with a poor prognosis in bone-mCRPC but appear to predict responses to docetaxel plus atrasentan.

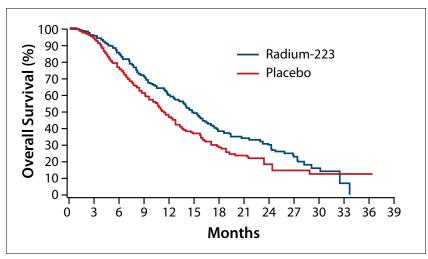


Figure 4. Overall survival in the ALSYMPCA trial. Data from Parker C et al. *J Clin Oncol* (ASCO Annual Meeting Abstracts) 2012;30(suppl): Abstract LBA4512.

to gain less benefit from radium-223 than patients with a higher serum ALP. Radium-223 also showed a similar outcome according to prior docetaxel use and current bisphosphonate use.

Radium-223 was also associated with a significant improvement over

placebo in the median time to first skeletal-related event (12.2 vs 6.7 months; HR, 0.64; 95% CI, 0.52–0.78; *P*<.0001) and other secondary endpoints, including time to total ALP progression, time to PSA progression, ALP response, and ALP normalization.

The analysis presented at the 2012 AUA meeting reported a significant delay in the median time to first skeletal-related event with radium-223 versus placebo (13.5 vs 8.4 months; HR, 0.61; 95% CI, 0.46–0.81; P=.0005). 3 This improvement reflected significant delays in the time to first pathologic bone fracture (HR, 0.45; P=.013), spinal cord compression (HR, 0.44; P=.016), and requirement for external beam radiation therapy (HR, 0.65; P=.0038). Requirements for surgical intervention were uncommon in both groups.

In regards to safety, radium-223 did not appear to increase the risk of hematologic adverse events aside from a small increase in grade 3/4 throm-bocytopenia (6% vs 2% with placebo) and grade 3/4 neutropenia (2% vs 1%). Grade 3/4 anemia was reported in 13% of patients in each arm.⁴ Radium-223 was associated with an increased incidence of any-grade diarrhea (25% vs 15%) and vomiting (19% vs 14%).⁴

The investigators concluded that, based on the significant improvement in overall survival and skeletal-related adverse events, as well as a favorable safety profile, radium-223 may provide a new standard treatment for patients with CRPC with bone metastases.

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Commentary

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istorically, there have been few treatment options for patients with castrate-resistant prostate cancer (CRPC), with or without radiologically confirmed disease. There has recently been a tremendous resurgence in therapeutic options for these patients. A landmark breakthrough was the understanding that androgen suppression effected significant clinical remission for androgen-sensitive prostate cancer cells. However, it was not until 2004 that docetaxel became the first chemotherapeutic agent approved by the US Food and Drug Administration (FDA) to prolong life for men with metastatic CRPC

(mCRPC).1 CRPC had previously been known as hormone-refractory or androgen-independent prostate cancer. The term CRPC is now internationally accepted as it addresses prostate-specific antigen (PSA) serum levels as well as radiographic progression in the setting of patients who have successfully received first-line androgen-suppressive therapies, including either a luteinizing hormone-releasing hormone (LHRH) agonist or antagonist, or a bilateral orchiectomy. CRPC patients are still sensitive to hormone-targeted therapeutics, as shown in studies presented at the 2012 American Urological Association (AUA) and 2012 American Society of Clinical Oncology (ASCO) annual meetings. There are no uniformly accepted guidelines of care for patients who have a rising PSA, who have received androgen-suppressive therapy, and who have no evidence of radiologic disease. Several studies presented at the AUA and ASCO meetings provided additional data regarding new therapeutic trials, as well as the recently approved immunotherapy sipuleucel-T.

There have been many exciting developments in CRPC, in terms of oral molecules, immunotherapeutics, and novel radioisotopes; in addition, data were presented to further interpret the impact of immunotherapy. Now is a very promising time for the advanced prostate cancer patient who is being appropriately monitored and treated by urologists, medical oncologists, and radiation oncologists.

ABSTRACT SUMMARY Cabozantinib (XL184) in Chemotherapy-Pretreated Metastatic Castration Resistant Prostate Cancer (mCRPC): Results From a Phase II Nonrandomized Expansion Cohort (NRE)

This nonrandomized expansion study of a phase II trial (Abstract 4516 from the 2011 ASCO meeting) enrolled patients with mCRPC previously treated with docetaxel with documented bone metastases and radiographic progression within 6 months of their last taxane dose (ASCO Abstract 4513). The study sequentially evaluated cabozantinib at 2 doses: 100 mg/day and 40 mg/day. Data were presented for the 100-mg cohort (n=93). The median age was 67 years (range, 46-85 years), and 73% had received at least 2 prior regimens for CRPC. The primary endpoint was bone scan response. In the 93 evaluable patients, cabozantinib was associated with a bone scan response rate of 67%; 4% were complete responses, defined as a 100% reduction in bone scan lesion area. The median duration of response was 5.4 months (range, 5.0-6.9 months). The median change in bone scan lesion area was a 60% reduction. Of 35 evaluable patients with measurable soft tissue lesions, the PR rate was only 3%, although 80% had evidence of tumor regression. PSA declines were observed in 36% of patients, although changes in PSA level were sometimes discordant with clinical benefit. Cabozantinib also appeared to reduce pain in patients with significant pain at baseline, and it improved bone biomarkers and reduced circulating tumor cell counts. The most common grade 3/4 adverse events were fatigue (28%), diarrhea (11%), nausea (10%), and hypertension (9%). Hand-foot syndrome of any grade occurred in 30% of patients. The majority of patients (84%) required at least 1 dose reduction due to adverse events.

Studies Presented at the AUA and ASCO Meetings

Cause-specific prostate cancer mortality is the second leading cause of metastatic tumor-related death in the United States.² It has been well established that certain populations in the United States, for example, African American menparticularly those living in metropolitan areas or the southeast of the United States—have a markedly higher risk of mortality from prostate cancer.3 At the AUA meeting, Brian K. McNeil, MD, presented data from a study that examined the importance of screening for prostate cancer in underserved populations.4 The study found that metastatic prostate cancer places a significant burden on the patient and overall economy, and that the increased mortality may be higher in underserved populations and

exacerbated if screening is not accessible. Other studies are needed to ensure that the recent recommendations from the US Preventive Services Task Force (USPSTF) regarding the benefits of screening are not applied uniformly to all populations, specifically underserved men and those who are at high risk for developing prostate cancer, such as the African American community.

At the 2012 AUA meeting, Leonard Gomella, MD, presented a statistical analysis attempting to better understand the potential therapeutic influence on survival in the IMPACT (9902B; Immunotherapy for Prostate Adenocarcinoma Treatment) trial, an mCRPC trial with a prespecified crossover design.⁵ The IMPACT trial was the first study to show the survival benefit of an immunotherapy in any advanced solid tumor, and led to FDA approval of sipuleucel-T in April 2010.6 Patients who received sipuleucel-T had a median overall survival benefit of 4.1 months as compared with patients in the control arm (hazard ratio [HR], 0.77). A majority of patients within the control arm received 3 infusions of an autologous cellular therapy (APC8015F) produced from cells frozen at the time of control product generation (ie, the crossover population). Another group of patients in the control arm did not receive their cryopreserved cells and APC8015F, but rather the standard of care per their physician investigator (ie, non-crossover control arm). The retrospective statistical analysis was performed to identify any benefit conferred by the crossover therapy. The Kaplan-Meier curve from the original phase III trial assumed that there was zero effect of the crossover arm. The analysis attempted to address, via the rank preserving structural failure time (RPSFT) statistical model, an estimate of various impacts of that crossover arm, assuming ranges from 0% effectiveness to 100% effectiveness with regard to potency of the APC8015 survival benefit. When assuming 100% effectiveness of APC8015, the crossover treatment conveyed a possible survival

ABSTRACT SUMMARY A Randomized Phase II Study of OGX-427 Plus Prednisone (P) Versus P Alone in Patients (pts) With Metastatic Castration Resistant Prostate Cancer (CRPC)

Initial results of a randomized phase II study comparing OGX-427 plus prednisone versus prednisone alone in patients with chemotherapy-naïve progressive mCRPC were presented (ASCO Abstract 4514). Patients were randomly assigned to OGX-427, administered at 600 mg for 3 loading doses in week 1, followed by 1,000 mg weekly for 24 weeks, plus prednisone 5 mg twice daily (n=22) or prednisone 5 mg twice daily alone (n=20). Patients in the control arm could cross over to OGX-427 plus prednisone upon disease progression; 50% had crossed over at the time of the current analysis. There were some differences in baseline characteristics with OGX-427 plus prednisone versus prednisone alone, including median age (66 years vs 72 years), presence of lung metastases (14% vs 0%), elevated LDH (36% vs 15%), and elevated alkaline phosphatase (32% vs 10%). At treatment week 12, 71% of patients in the OGX-427 plus prednisone arm were progression-free, compared with 40% of patients in the prednisone arm. A PSA decline of at least 50% was observed in 50% of patients receiving OGX-427 plus prednisone versus 20% with prednisone alone. Among the subset of patients with measurable disease, the ORR was 44% (including 1 CR) with OGX-427 plus prednisone and 0% with prednisone alone. Substantial declines in CTC count were seen in the OGX-427 arm. OGX-427 was associated with an increased risk of infusion-type reactions, although no grade 3/4 infusion reactions occurred in more than 1 patient. Grade 3/4 laboratory abnormalities occurring in more than 1 patient included lymphopenia (18%) and hyperglycemia (14%).

benefit of more than 12 months in selected populations. The overall retrospective statistical analysis suggested that the survival benefit of treatment with sipuleucel-T may have approached 7.8 months, as opposed to the 4.1 months previously reported, which assumed no survival benefit from the crossover population treatment effect.

An additional retrospective analysis of the IMPACT study was presented by Gerald Chodak, MD, at this year's ASCO meeting.⁷ This analysis divided patients into 4 different quartiles based upon their baseline screening PSA levels upon study entry. Interestingly, the analysis suggests that patients with a lower PSA level—which usually correlates with lower tumor burden—did markedly better with regard to overall survival. This finding supports the intuitive assumption that patients who receive therapy earlier in their mCRPC course, who have lower tumor burden and perhaps

a more intact and responsive immune system, may have greater benefit from treatment. This analysis suggests that clinicians who are interested in providing immunotherapy might consider screening their patients more proactively once CRPC is established, and thereby try to identify those who might benefit from earlier administration of sipuleucel-T in the M1CRPC state.

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) study were presented at both the AUA 2012 and ASCO 2012 meetings. 8,9 Enzalutamide, formerly known as MDV3100, is an oral therapeutic administered once daily; steroids are not required. It can be taken with or without food. Of note, enzalutamide was associated with the longest overall survival advantage in

a postchemotherapy phase III trial to date—4.8 months. The adverse event profile was very acceptable. The patients had some increase in mild fatigue, while rates of severe fatigue did not differ from the placebo group. There were no significant serologic abnormalities in terms of liver function or electrolytes. In the MDV3100 arm, approximately 50% of patients had a greater than 50% decrease in prostate-specific antigen (PSA), and about 25% of patients had a greater than 90% decline in PSA, suggesting its therapeutic benefit for mCRPC patients postchemotherapy.

Enzalutamide competitively inhibits binding of androgens to the androgen receptor, inhibits androgen receptor nuclear translocation, and inhibits association of the androgen receptor with DNA binding.¹⁰ Enzalutamide provides more potent competitive binding to the androgen receptor than earlier-generation lutamides, such as bicalutamide and flutamide. It also prevents translocation of the androgen receptor to the nucleus, which has further implications regarding DNA binding and promotion of tumor cells. Enzalutamide is a once daily oral therapy that appears to be very well tolerated. It appears to have a significant impact not only on survival, but also on PSA and radiographic progression. A new drug application for enzalutamide has been filed with the FDA and has received a priority review.¹¹ It is possible that this novel, oral drug therapy will be approved by the end of this year. An additional trial of enzalutamide that has just finished accrual is examining this agent in the prechemotherapy setting. If approved, enzalutamide should have strong clinical appeal for both the medical oncology and urology communities due to its efficacy and tolerability.

The results of a phase III study, COU-AA-302, of abiraterone acetate plus prednisone versus control in patients with asymptomatic mCRPC were presented at the ASCO meeting. ^{12,13} This trial addressed an area of unmet need. Sipuleucel-T is approved for patients who have asymptomatic or minimally symptomatic M1CRPC. Docetaxel is

an approved chemotherapy for these patients. However, most patients who receive docetaxel are symptomatic. In the 302 trial, the treatment arms consisted of abiraterone acetate plus prednisone and placebo plus prednisone, randomized 2:1. The interim results demonstrated that the addition of abiraterone acetate had a very significant impact on radiographic PFS. 12,13 There were 2 co-primary endpoints: radiographic PFS and overall survival. The radiographic PFS was highly statistically significant, as was the impact on the secondary endpoints of the trial, such as time to PSA progression. The co-primary endpoint of overall survival just missed hitting statistical significance by .0001 tenth of a calculation. Additional analysis is pending, awaiting further events, and may have a very important impact on our treatment options for the asymptomatic mCRPC patient. The COU-AA-302 data have been submitted for FDA review so that the indication of abiraterone acetate plus prednisone can be expanded to include the asymptomatic, prechemotherapy mCRPC population. If approved for this patient population, abiraterone acetate with prednisone will provide another important therapeutic option for treatment of patients with asymptomatic to minimally symptomatic M1CRPC.

Data from the ALSYMPCA study were presented at both the AUA 2012 and ASCO 2012 meetings.14,15 Historically, various isotopes have been used to ameliorate pain and presumably delay the onset of skeletal-related events associated with bone metastasis in prostate cancer. Previously approved radioisotope therapeutics have been associated with myelosuppression due to their bone marrow depth of penetration, which can affect the future ability to effectively use cytotoxic chemotherapy later in the course of disease management. Previous radioisotope trials have shown that these therapies can reduce skeletal-related events, but have not demonstrated an overall survival benefit in phase III trials. 16 The ALSYMPCA trial is a landmark success for isotope therapeutics, as it is the first trial to demonstrate that a radioisotope—an alpha-isotope as opposed to traditional beta/gamma isotopes improved overall survival in patients with CRPC. The first interim analysis of the ALSYMPCA trial, presented at the 2010 meeting of the European Society for Medical Oncology (ESMO), showed an overall survival benefit of 2.8 months, 17 which increased to 3.6 months when further interim analysis results were presented at the ASCO meeting.¹⁵ The accrual population included patients with progressive disease who either received docetaxel or were considered unfit for docetaxel. The safety and tolerability profile appears to be well suited for patients with advanced disease. The ratio of adverse and severe adverse events was comparable between the treatment and the control groups, and, notably, there was minimal myelosuppression. The ALSYMPCA trial explored an agent with a novel mechanism of action that may be complementary to already approved and pending mCRPC therapeutics.

SWOG 9346 was an international phase III trial of intermittent androgendeprivation therapy versus continuous androgen deprivation in patients with hormone-sensitive metastatic prostate cancer.18 This trial began 17 years ago, involving many sites in order to achieve the volume of accrual and the timeframe to allow for meaningful interpretation of the course of disease and strategies for androgen suppression for patients with metastatic and androgen-sensitive disease upon trial screening. The trial used arbitrary cutoff points to determine when to reinstitute androgen-deprivation therapy; for most patients, the cutoff was 20 ng/dL. The study was powered for noninferiority, and it found that intermittent androgen-deprivation therapy was statistically inferior compared to continuous androgen-deprivation therapy. Somewhat counterintuitively, patients who had less burden of disease did worse than patients who had higher burden of disease. Although some finer points of the inclusion and exclusion criteria warrant review, this phase III trial is the first prospectively performed study to address the ongoing question of intermittent ver-

sus continuous therapy. For many years, preclinical models had appeared to suggest that intermittent therapy might have an advantage in preventing the onset of CRPC and, consequently, mortality. 19 In the SWOG 9346 trial, continuous therapy improved survival as compared with intermittent therapy.¹⁸ Notably, the overall length of survival for all patients in the study was, on average, approximately 5 years. Overall survival was 5.8 years in the continuous therapy group and 5.1 years in the intermittent therapy group. For the advocacy community and for patients who present with advanced disease, the improvement in overall survival is welcome news. The fact that the median survival was approximately 5 years should provide optimism to patients who receive this initial diagnosis, as previous data suggested median survival rates of approximately 3 years for this same patient population. This overall improved survival may also reflect the impact of the additional therapies that have been developed during the course of this trial to prolong the life of these patients who unfortunately present with very advanced disease.

A study for the prevention of bone metastases, presented by Matthew Smith, MD at the AUA meeting, tested whether denosumab could delay the development of bone metastasis in men with CRPC.20 There is a decided unmet need for the M0CRPC population. There is no therapy—whether it be administered orally, intravenously, intramuscularly, or subcutaneously that has level 1 evidence to support its use in delaying or preventing bone metastases. The trial by Smith and colleagues compared monthly subcutaneous administration of denosumab versus a placebo-injection. Denosumab was associated with a statistically significant improvement in the prevention of bone metastases as well as symptomatic bone metastases in high-risk patients. The median time to multiple and/or symptomatic bone metastases was 37 months in the placebo group and 44.6 months in the denosumab group. These data are clinically significant. Additional trials

are being considered due to the FDA's recent failure to approve denosumab in the M0CRPC setting.21 Denosumab 120 mg monthly has been approved for the prevention of skeletal-related events in patients with existing bone metastasis, and denosumab 60 mg given every 6 months has been approved for men receiving androgen-deprivation therapy to prevent bone demineralization and decrease the risk of fracture. Patients with M0CRPC fall between these categories and certainly represent a significant unmet therapeutic need. Although there remains some discussion regarding the benefit shown in this study, the primary and secondary outcomes were statistically significant and suggest a strong clinical impact, especially for patients who have higher PSA levels or more rapid PSA doubling times.

Cabozantinib appears to be a unique oral agent that has inhibition of MET and vascular endothelial growth factor receptor-2 (VEGFR2) as its assumed pathway and mechanism of action.22 A phase II trial presented at the 2011 ASCO meeting showed that cabozantinib has demonstrated remarkable bone scan resolution, as well as symptomatic pain relief and disease control, independent of PSA changes.²² A phase II trial of cabozantinib presented at the 2012 ASCO meeting showed significant relief of pain, a correlating change for the better according to bone scan, and even some reduction of the bone tumor markers in circulating tumor cells.²³ Given the impact of cabozantinib on pain and bone scans, as well as its oral administration, it is an extremely promising agent that is undergoing further study in both pre- and postchemotherapy populations. With its apparent unique targeted pathways, it may provide another option for the treatment of advanced prostate cancer patients with symptomatic bone metastases.

Nomograms were the focus of a study presented by Michael W. Kattan, MD, at the ASCO meeting.²⁴ There are several currently available nomograms to assist with prostate cancer

prognostication. These nomograms suggest that some physicians may overor underestimate disease prognosis. Prior studies have supported the use of nomograms as an integral part of the clinical decision process in the prostate cancer setting; nonetheless, there is a lack of consensus regarding the final validation of these nomogram models from a guideline adherency standpoint and their routine application in clinical practice. I believe that physicians who treat a large number of prostate cancer patients, either newly diagnosed or with advanced disease, would welcome a user friendly and validated nomogram that might diminish the need for unnecessary treatments or redundant testing, and, likewise, would prompt more aggressive therapy when warranted.

Acknowledgment

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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 baq.
- 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 ≥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 \leq 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 ≥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 ≥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.** Data on file. Dendreon Corporation.

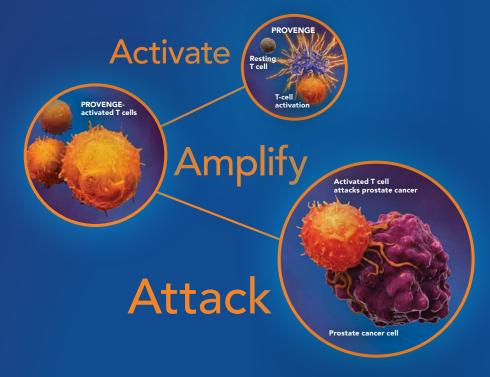


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In advanced prostate cancer

TREAT EARLY WITH PROVENGE TO



EXTEND SURVIVAL

PROVENGE activates the immune system to fight advanced prostate cancer

> 2 years

PROVENGE extends median survival beyond 2 years¹

• Reduced the risk of death by 22.5% vs the control arm $(P=0.032)^1$

1.5%

PROVENGE provides a safety profile you can manage

- 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

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 included 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.

