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A SPECIAL MEETING REVIEW EDITION

Highlights in Advanced Prostate Cancer From the 2014 American Society of Clinical Oncology Genitourinary Cancers Symposium

A Review of Selected Presentations From the 2014 American Society of Clinical Oncology Genitourinary Cancers Symposium • January 30-February 1, 2014 • San Francisco, California

Special Reporting on:

- Enzalutamide in Men With Chemotherapy-Naive Metastatic Prostate Cancer (mCRPC): Results of Phase III PREVAIL Study
- Antigen Spread and Survival With Sipuleucel-T in Patients With Advanced Prostate Cancer
- Results From a Phase 3, Randomized, Double-Blind, Multicenter, Placebo-Controlled Trial of Orteronel (TAK-700) Plus Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer (mCRPC) That Has Progressed During or Following Docetaxel-Based Therapy (ELM-PC 5 Trial)
- Impact of Prior Radiation Treatment (tx) on Sipuleucel-T (sip-T) Product Parameters in PROCEED Patients (pts)
- 1.5-Year Post-Treatment Follow-Up of Radium-223 Dichloride (Ra-223) in Patients With Castration-Resistant Prostate Cancer (CRPC) and Bone Metastases From the Phase 3 ALSYMPCA Study
- Sipuleucel-T in Metastatic Castration-Resistant Prostate Cancer (mCRPC) Patients ≥80 Years-Old: Data From PROCEED

PLUS Meeting Abstract Summaries

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Enzalutamide in Men With Chemotherapy-Naive Metastatic Prostate Cancer (mCRPC): Results of Phase III PREVAIL Study

Enzalutamide is an androgen-receptor agonist that inhibits the receptor's nuclear translocation and DNA binding, thus preventing androgen-induced signaling.[1] The drug was approved by the US Food and Drug Administration (FDA) based on results from the phase 3 AFFIRM (Safety and Efficacy Study of MDV3100 in Patients With Castration-Resistant Prostate Cancer Who Have Been Previously Treated With Docetaxel-Based Chemotherapy) trial of enzalutamide vs placebo in men with metastatic castration-resistant prostate cancer (CRPC) who had received prior chemotherapy.[2] In this trial of 1199 patients, enzalutamide extended the primary endpoint of median overall survival (OS) to 18.4 months vs 13.6 months in the placebo control arm (*P*<.001) and extended median radiographic progression-free survival (PFS) to 8.3 months vs 2.9 months (*P*<.001).

Based on the positive results in men who had received chemotherapy, the international, double-blind, randomized PREVAIL (A Safety and Efficacy Study of Oral MDV3100 in Chemotherapy-Naive Patients With Progressive Metastatic Prostate Cancer) trial was designed to examine the efficacy and safety of enzalutamide in patients with asymptomatic or minimally symptomatic metastatic CRPC who had not received chemotherapy and whose disease had progressed following hormonal therapy.[3] The trial had 2 primary endpoints—OS and radiographic PFS—and included 2 OS analyses: an interim analysis after 516 events and a final analysis after 765 events. One analysis for PFS was planned after 410 events.

Enrollment was completed throughout approximately 24 months at 207 centers in 22 countries, with 1717 patients randomized 1:1 to enzalutamide (160 mg daily) or placebo. In October 2013, after the first 540 deaths, the independent data monitoring committee concluded that enzalutamide conferred a significant benefit with respect to both primary endpoints. The committee therefore recommended halting the study and offering enzalutamide to patients enrolled in the placebo arm.

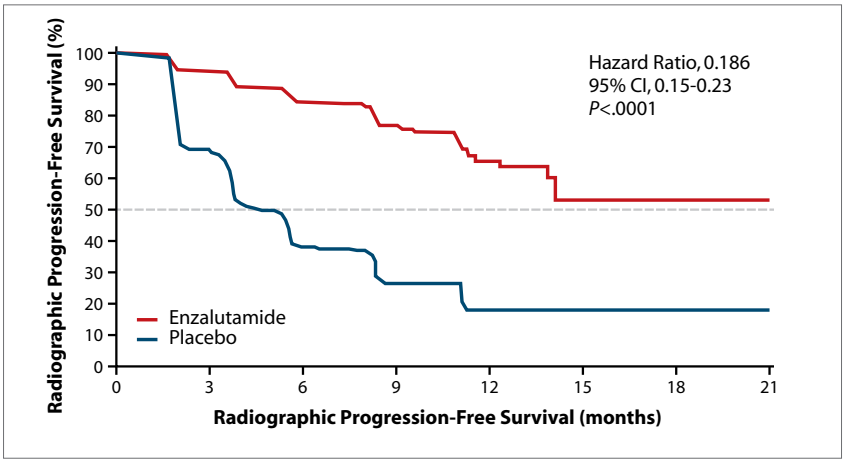

Figure 1. In the phase 3 PREVAIL trial, enzalutamide significantly delayed the progression of metastatic disease as demonstrated by a superior median radiographic progression-free survival as compared with placebo in chemotherapy-naive patients with progressive metastatic prostate cancer. PREVAIL, A Safety and Efficacy Study of Oral MDV3100 in Chemotherapy-Naive Patients With Progressive Metastatic Prostate Cancer.

Adapted from Beer TM et al. ASCO GU abstract LBA1. *J Clin Oncol.* 2014;32(4)(suppl).[3]

Median treatment duration was 16.6 months for the active drug vs 4.6 months for the placebo. The study drug significantly delayed the progression of metastatic disease as demonstrated by an 81% improvement in the risk of progression or death. The median radiographic PFS was not reached in the enzalutamide arm (95% CI, 13.8 months-not reached) vs 3.9 months in the placebo arm (95% CI, 0.15-0.23; hazard ratio [HR], 0.186; *P*<.0001; Figure 1). Subgroup analysis showed a radiographic PFS benefit for patients with visceral disease.

The study drug also improved OS, with a 29% reduction in the risk of death (32.4 months vs 30.2 months; HR, 0.706; 95% CI, 0.60-0.84; *P*<.0001). However, because approximately two-thirds of patients in both arms were still on therapy, the OS results reflect data from only 3.2% of study patients. The analyses were potentially confounded by the fact that, after progressing on the trial, nearly twice as many patients in the placebo arm were treated with drugs known to increase survival. Moreover, patients in the placebo arm progressed more quickly than those receiving enzalutamide; therefore, in the placebo arm, 56% of patients received docetaxel and 46% of patients received abiraterone after progression. Enzalutamide improved OS across all patient subsets examined. The treatment led to a 59% reduction in measurable disease, including 20% complete responses and 32% partial responses. Patients treated

with enzalutamide also showed a median 17-month delay in the need for cytotoxic chemotherapy (HR, 0.35). Patients received chemotherapy for a median 28 months in the enzalutamide arm and a median 10.8 months in the placebo arm. Enzalutamide also yielded a longer time to progression of prostate-specific antigen (PSA) levels (HR, 0.17) and a longer time to deterioration of quality of life (HR, 0.625).

Safety data showed that enzalutamide was well tolerated. Of note, because the patients receiving the study drug received treatment for 3 times longer than patients in the placebo arm, the time during which toxicity data were collected differed accordingly for the 2 arms. Serious adverse events (AEs) were observed in 32% of enzalutamide patients vs 27% of placebo patients, with grade 3 or higher AEs observed in 43% vs 37% of patients, respectively. However, the median time until the first grade 3 or higher AE was longer in the enzalutamide arm (22 months vs 13 months, respectively). Treatment discontinuation was reported in 6% of patients in each arm. The most common AEs of any grade that were more frequent in patients receiving the study drug were fatigue, back pain, constipation, and arthralgias. Grade 3 or higher AEs occurred in 2.8% of enzalutamide patients vs 2.1% of placebo patients, and grade 3 hypertension occurred in 6.8% vs 2.3% of patients, respectively. One patient in each arm had a seizure, and both of these patients had a history of seizures prior to the study that was not disclosed at the time of enrollment.

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Antigen Spread and Survival With Sipuleucel-T in Patients With Advanced Prostate Cancer

Sipuleucel-T efficacy is predicated on the ability to stimulate the patient's antigen-presenting cells (APCs) to recognize the prostatic acid phosphatase tumor antigen, which is present in 95% of prostate tumors.[1] The therapy's resulting tumor cell lysis may lead to the release of secondary tumor antigens that effect a broader immune response, a phenomenon known as *antigen spread*. In the IMPACT trial, patients treated with sipuleucel-T produced consistent immunoglobulin G (IgG) responses against secondary antigens 3 to 4 months after treatment.[2] In contrast, no IgG responses against secondary antigens were observed in the control arm. An analysis of patient serum collected during the IMPACT trial aimed to assess the immune response against secondary tumor antigens and determine the relationship between secondary immune response and clinical outcome.[3] The study analyzed serum taken at baseline, 6 weeks, 14 weeks, and 26 weeks after treatment initiation. IgG response was defined as a minimum 2-fold increase in the antigen-specific level relative to baseline by testing on protein microarrays. The relationship between IgG response and OS was assessed using a Cox regression model adjusted for prior bisphosphonate use and baseline prognostic factors, such as

ABSTRACT SUMMARY Effect of Prior Abiraterone (ABI) or Enzalutamide (ENZ) on Sipuleucel-T (sip-T) Manufacture in PROCEED Patients (pts)

The PROCEED registry does not exclude patients based on prior therapy (ClinicalTrials.gov identifier: NCT013068900). An analysis aimed to evaluate the effects of prior abiraterone acetate or enzalutamide on sipuleucel-T product parameters (Abstract 185). Of 1376 patients enrolled as of May 2013, 108 (7.8%) had received prior abiraterone and 58 (4.2%) had received prior enzalutamide. Median PSA levels and median lactose dehydrogenase levels were higher for abiraterone patients (20.3 ng/mL; 201.0 U/L) compared with enzalutamide patients (12.9 ng/mL; 175.0 U/L) and patients who had received neither treatment (16.0 ng/mL; 187.0 U/L). A higher proportion of abiraterone patients had received prior chemotherapy compared with enzalutamide patients (43.5% vs 29.3%). As compared with patients who had received neither abiraterone nor enzalutamide, the patients who had received one or the other were slightly younger (70 years vs 72 years), but they appeared to have more advanced disease based on lower hemoglobin levels and more extensive bone disease. A greater proportion had received prior chemotherapy (37.5% vs 12.3%). At weeks 0, 2, and 4, APC and total nucleated cell counts were lower for abiraterone patients compared with enzalutamide patients and the abiraterone-naive and enzalutamide-naive patients. However, the extent of APC activation was comparable for the 3 patient groups at weeks 0, 2, and 4. Therefore, prior treatment with abiraterone acetate or enzalutamide did not appear to compromise immunologic stimulation during preparation of sipuleucel-T.

Table 1. Confirmation of Secondary Antigen Response in Patient Serum From the ProACT Trial

Secondary Tumor Antigen	Proportion of Responding Patients (%)	*P* Value
ERAS	38%	.0007
KLK2	27%	.0031
KRAS	27%	.0034

ProACT, Prostate Advanced Cancer Treatment. Data from Drake CG et al. ASCO GU abstract 88. *J Clin Oncol*. 2014;32(4)(suppl).[3]

levels of serum PSA and lactate dehydrogenase, the presence or absence of bone lesions, and Gleason score.

IgG responses to 244 secondary antigens were assessed in serum samples taken from 93 patients in the sipuleucel-T arm and 40 patients in the control arm. From these 244 antigens, 10 candidate secondary antigens in 2 categories were selected for confirmation. Antigens that elicited a response at week 14 and had a known relevancy to cancer development included KRAS, ERAS, KLK2, LGALS8, and TSPAN13. Antigens that showed the highest average increase at week 14 in the sipuleucel-T arm relative to baseline, regardless of relevance to cancer development, included LGALS3, ECE1, ANPEP, CACNG1, and FBXO6. Seven of these candidate genes were confirmed using a bead-based suspension array assay that showed a significant increase in IgG response at week 14 ($P<.01$). The outcomes were validated by analyzing patient serum samples from the ProACT (Prostate Advanced Cancer Treatment) trial that showed a significant increase in IgG response from baseline to 4 months after treatment (Table 1).[3,4] An IgG response at week 14 to either the primary antigen (prostatic acid phosphatase) or any of the 7 antigens alone was not significantly associated with OS. However, IgG responses to prostatic acid phosphatase as well as 2 or more secondary antigens were associated with improved OS ($P<.01$; HR, <0.4; Figure 2). The authors concluded that the new methodology could facilitate the identification of serum biomarkers as a surrogate for assessing in vivo therapeutic effects in patients with prostate cancer or other malignancies.

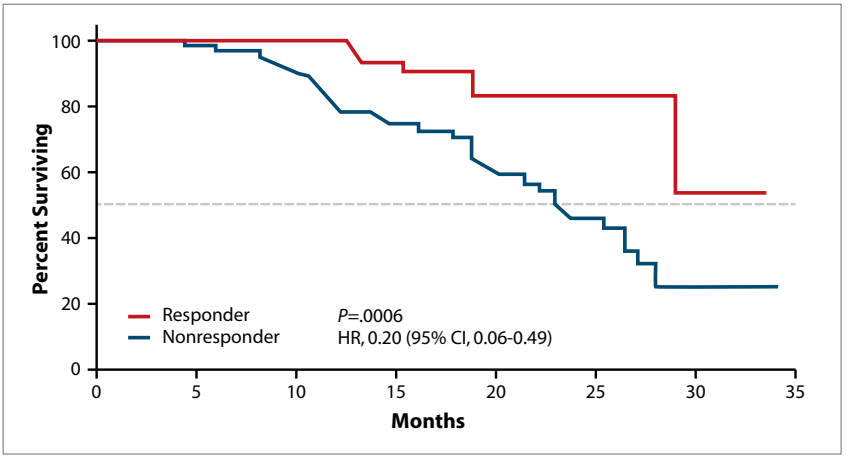

Figure 2. In an analysis of data from the phase 3 IMPACT trial of sipuleucel-T, improved overall survival was seen in patients who showed an immunoglobulin G response to the primary antigen and any 3 secondary antigens.

IMPACT, Immunotherapy Prostate Adenocarcinoma Treatment. Adapted from Drake CG et al. ASCO GU abstract 88. *J Clin Oncol*. 2014;32(4)(suppl).[3]

ABSTRACT SUMMARY An OPEN-Label PHASE II Clinical Trial of the RXR Agonist IRX4204 in Taxane-Resistant, Castration-Resistant Metastatic Prostate Cancer (CRPC)

IRX4204 is a potent, selective, oral agonist of the retinoid X receptor (RXR) pathways. A phase 1 trial of IRX4204 included 1 prostate cancer patient, who showed a sustained reduction in PSA of more than 90% from baseline and a partial response lasting more than 7 months (IRX4204. http://io-therapeutics.com/programs/4204-2/). An open-label phase 2 trial was initiated to evaluate the safety and efficacy of IRX4204 in men with prostate cancer (Abstract 169). The trial enrolled 23 men with metastatic CRPC who had failed a taxane or declined chemotherapy and had evidence of biochemical or radiographic progression. Evidence of study drug benefit was defined as PFS greater than 56 days, a 50% PSA decrease, or partial response or complete response as assessed by the Response Evaluation Criteria In Solid Tumors. Patients received IRX4204 at a dosage of 20 mg daily. The study drug was generally well tolerated, with no related serious AEs. There were manageable decreases in thyroid-stimulating hormone and increases in triglycerides, both of which are known AEs of RXR agonists. Fifteen patients met the study's criterion for PFS benefit. PFS beyond 112 days was observed in 9 patients (39%). One patient continued on IRX4204 for more than 14 months without evidence of disease progression. PSA reduction of at least 50% was observed in 3 patients (13%); in 1 patient, this reduction exceeded 90%.

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Results From a Phase 3, Randomized, Double-Blind, Multicenter, Placebo-Controlled Trial of Orteronel (TAK-700) Plus Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer (mCRPC) That Has Progressed During or Following Docetaxel-Based Therapy (ELM-PC 5 Trial)

Cytochrome P450c17, which is also known as *17,20 lyase*, is a critical enzyme for androgen biosynthesis and is upregulated in metastatic CRPC. It has been validated as a prostate cancer target by phase 3 trials that investigated abiraterone acetate in men with metastatic CRPC who were chemotherapy-naive or who had progressed on prior docetaxel.[1,2] Orteronel (TAK-700) is an investigational, nonsteroidal, reversible, selective inhibitor of 17,20 lyase. Phase 1 and 2 trials demonstrated the drug's safety and efficacy in patients with metastatic CRPC, and in a phase 1/2 trial of patients with nonmetastatic CRPC, treatment with orteronel led to significant and durable declines in levels of PSA.[3]

Dr Robert Dreicer presented results from the double-blind, multicenter, placebo-controlled, phase 3 ELM-PC-5 (Evaluation of the Lyase Inhibitor Orteronel in Metastatic Prostate Cancer) trial of orteronel in men with previously treated prostate cancer.[4] The study enrolled 1099 patients with metastatic CRPC that had progressed after 1 or 2 prior cytotoxic chemotherapeutic regimens, one of which had to include docetaxel. Patients were randomized 2:1 to receive prednisone (5 mg twice daily) plus either orteronel (400 mg twice daily) or placebo. The study's primary endpoint was OS, with key secondary endpoints of radiographic PFS based on Prostate Cancer Working Group 2 criteria, PSA response at 12 weeks, and pain response at 12 weeks.[5]

Recruitment occurred in 260 centers from 42 countries over 2 years. Patients were stratified by region and the amount of pain they were experiencing (as assessed by a Brief Pain Inventory [short form] score of ≤4 vs >4). Interim analyses were planned after 50% and 67% of anticipated events. The second interim analysis occurred after 512 deaths or 80% of anticipated deaths. The analysis showed that the OS rates had crossed the prespecified futility boundaries, and the trial was unblinded based on a recommendation from the independent data monitoring committee.

Baseline demographics were well balanced between the 2 arms. Patients in the orteronel-plus-prednisone arm received a median 6.2 treatment cycles vs 5.0 in the placebo arm. Treatment discontinuation rates in the experimental arm vs the placebo arm were, respectively, 26% vs 21% for AEs; 18% vs 22% for disease progression; 13% vs 7% for withdrawal by subject; 10% vs 15% for symptomatic deterioration; 9% vs 13% for initiation of other antineoplastic therapy; and 4% vs 5% for other reasons. The median duration of therapy was 5.7 months (range, 0.03-26.4 months) for orteronel plus pred-

ABSTRACT SUMMARY Results of a Phase II Trial of Abiraterone Acetate (AA) Combined With Dutasteride (DUT) for Men With Metastatic Castration Resistant Prostate Cancer (mCRPC)

Abiraterone acetate increases survival in men with metastatic CRPC, but tumors eventually progress on therapy. A phase 2 study was conducted to identify mechanisms of drug resistance in men with metastatic CRPC treated with abiraterone acetate and dutasteride, a dual 5α reductase inhibitor (Abstract 126). The 40 enrolled patients initially received abiraterone acetate (1000 mg daily) and prednisone (5 mg daily); dutasteride (3.5 mg daily) was added after 2 months, and therapy was continued until radiographic progression. After a median follow-up of 13 months, 24 men (60%) had a PSA decline of at least 50% and 12 men (30%) had a decline of at least 90%. These declines were reached at a median of 1.4 months and 2.4 months, respectively. At the nadir, median PSA had declined by 78% to 6.3 ng/mL, which was reached at a median of 3.2 months from baseline. The majority of AEs were grade 1 or 2, with 3 patients (7.5%) experiencing a grade 3 AE and no grade 4 AEs reported. An increase in disease flares (defined as intensity and number of lesions) at 3 months vs baseline was observed in 8 patients (47%) with available computed tomography and bone scans. Flares improved by 6 months in 4 patients. In addition to these secondary endpoints, the primary endpoint of resistance will be evaluated by analyzing biomarkers in patients' serial tumor biopsies.

nisone vs 4.6 months (range, 0.3-27.0 months) for prednisone alone.

The most common AEs of any grade in the orteronel arm were nausea (42% vs 26% with placebo), vomiting (36% vs 17% with placebo), fatigue (29% vs 23% with placebo), and constipation (29% vs 18% with placebo). Drug-related AEs of grade 3 or higher occurred in 37% of patients who received orteronel vs 18% of patients in the control arm. Grade 3 or higher AEs of particular interest in the orteronel arm included increased lipase (13% vs <1% with placebo), increased amylase (8% vs <1% with placebo), and hypertension (3% vs 2% with placebo). Pancreatitis was rare, occurring in less than 1% of patients receiving the experimental drug. Although gastrointestinal toxicities were uncommon, they were the most frequent cause of treatment discontinuation. Rates of peripheral edema and hypokalemia were similar between the 2 arms.

The trial failed to meet its primary endpoint. Median OS was 17.0 months (95% CI, 15.2-19.9 months) in the orteronel-plus-prednisone arm vs 15.2 months (95% CI, 13.5-16.9 months) in the placebo arm (HR, 0.886; 95% CI, 0.739-1.062; *P*=.1898; Figure 3). However, prespecified regional analysis suggested that the OS results may have been confounded by the fact that more than half of patients in Europe and North America received poststudy therapy that included abiraterone, enzalutamide, and cabazitaxel vs 38% of patients in other parts of the world. Pooled results from the 397 non-European, non–North American patients yielded an OS difference of 15.3 months for orteronel plus prednisone vs 10.1 months for prednisone only (HR, 0.709; *P*=.019). Radiographic PFS was significantly prolonged in patients who received orteronel vs those who did not (8.3 months vs 5.7 months; HR, 0.76; *P*=.00038). Analysis of the non-European, non–North American subset of patients also showed a significant increase in patients who received orteronel vs placebo (6.7 months vs 5.2 months; HR, 0.66).

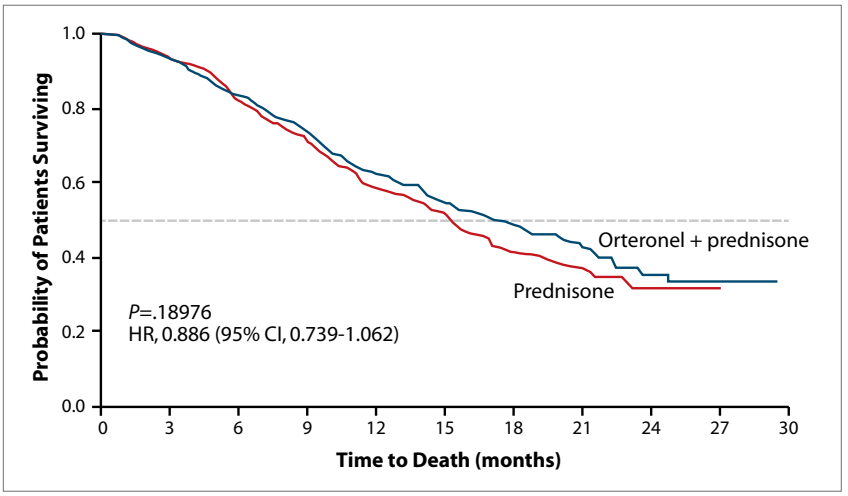

Figure 3. The phase 3 ELM-PC-5 trial of orteronel plus prednisone vs prednisone alone in men with metastatic prostate cancer failed to meet its primary endpoint of improved overall survival.

ELM-PC-5, Evaluation of the Lyase Inhibitor Orteronel in Metastatic Prostate Cancer; HR, hazard ratio. Adapted from Dreicer R et al. ASCO GU abstract 7. *J Clin Oncol.* 2014;32(4)(suppl).[4]

ABSTRACT SUMMARY Enzalutamide After Failure of Docetaxel and Abiraterone in Metastatic Castrate Resistant Prostate Cancer (mCRPC): Results From an Expanded Access Program

A key question in the treatment of metastatic CRPC involves the best sequencing of agents. To provide insight regarding feasible sequential treatments, this study examined outcomes in patients who received enzalutamide, as part of an expanded access program, after failing treatment with docetaxel and abiraterone (Abstract 188). The 23 patients showed a median biochemical PFS of 2.8 months and a median OS of 8.5 months. Nine patients (39.1%) showed sensitivity to enzalutamide, defined as a reduction in PSA of at least 50%, and 1 patient showed a PSA reduction of at least 90%. A correlation was observed between response to abiraterone and response to subsequent enzalutamide (r=0.45; P=.03). A PSA reduction of at least 50% was observed in 6 patients (60%) who were sensitive to abiraterone vs 3 patients (23%) who were insensitive to the drug. Abiraterone-sensitive patients also showed a trend toward improved biochemical PFS compared to abiraterone-insensitive patients (3.6 months vs 2.6 months; P=.18), as did patients who showed any PSA response to abiraterone compared with those who did not (3.7 months vs 1.2 months; P=.07).

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Impact of Prior Radiation Treatment (tx) on Sipuleucel-T (sip-T) Product Parameters in PROCEED Patients (pts)

Radiation treatment can suppress bone marrow function and, consequently, immune system function. The IMPACT trial therefore excluded patients who had received radiation treatment within 28 days of registration.[1] In contrast, the PROCEED registration study did not exclude patients who had received prior treatments, including chemotherapy or radiation.[2] Data from the PROCEED study may help determine whether prior radiation treatment affects the product characteristics of sipuleucel-T.

Dr Steven Finkelstein and colleagues presented preliminary results on baseline demographics and sipuleucel-T product parameters in patients who did or did not receive palliative radiation for bone metastases before treatment with sipuleucel-T.[3] Eligible patients had received sipuleucel-T treatment in a real-world setting within the previous 6 months. As of May 2013, there were 1244 patients with available data. Of these patients, 112 (9.0%) had received palliative radiation to bone metastases before sipuleucel-T treatment and 517 (41.6%) had received no prior radiation treatment. The remaining patients had received radiation treatment for other indications. To ensure that the compared groups were homogeneous and to compare the patients who had not received palliative radiation with those who had received prior radiation for bone metastases only, the 459 patients who received a radical prostatectomy were isolated for further study, thus yielding 44 patients in the palliative radiation group and 159 patients in the no palliative radiation group.

Median cumulative APC counts were similar in both groups (1.88×10^9 for palliative radiation vs 2.04×10^9 for no palliative radiation); however, palliative radiation patients had lower total nucleated cell counts (9.89×10^9 vs 12.09×10^9, respectively; P=.002; Figure 4) and reduced levels of APC activation (34.21 vs 38.51; P=.048). Patients in the palliative radiation group had generally worse baseline health, as reflected by the lower proportion with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 (61.4% vs 69.8%) and higher median levels of PSA (15.4 ng/mL vs 12.3 ng/mL), which may have contributed to the difference in cumulative APC activation. Similar proportions of patients in the 2 groups received all 3 sipuleucel-T infusions (93.2% for palliative radiation vs 95.0% for no palliative radiation; P=.707). The authors concluded that, in the real-world setting, prior palliative radiation therapy for bone metastases did not appear to inhibit successful production of sipuleucel-T; however, further studies to confirm the findings are needed.

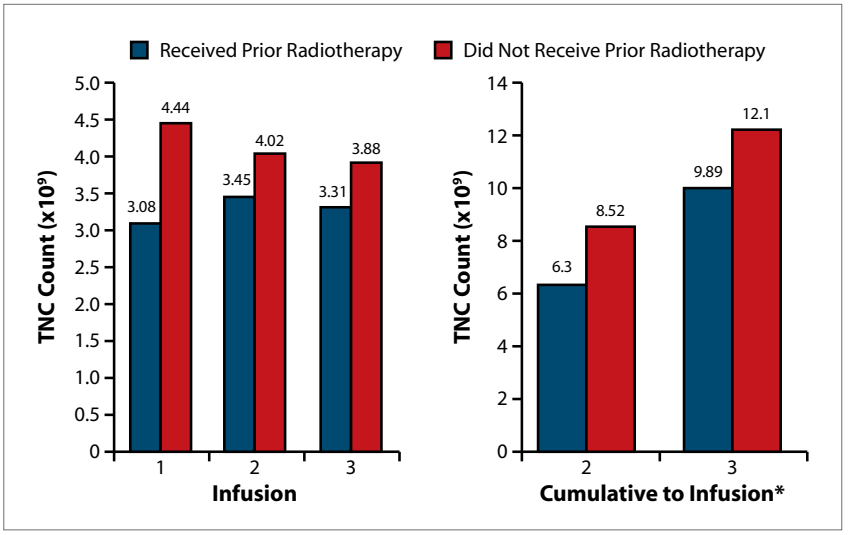

Figure 4. In an analysis of patients receiving sipuleucel-T in the PROCEED registry, total nucleated cell (TNC) counts were lower in patients who had received palliative radiation for bone metastases before treatment with sipuleucel-T than in patients who had not. *Cumulative counts from infusion 1 through to infusions 2 and 3. PROCEED, PROVENGE Registry for the Observation, Collection, and Evaluation of Experience Data.

Adapted from Finkelstein SE et al. ASCO GU abstract 183. *J Clin Oncol.* 2014;31(suppl 6).[3]

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3. Finkelstein SE, Nordquist LT, Dakhil SR, et al. Impact of prior radiation treatment (tx) on sipuleucel-T (sip-T) product parameters in PROCEED patients (pts) [ASCO GU abstract 183]. *J Clin Oncol.* 2014;31(suppl 6).

1.5-Year Post-Treatment Follow-Up of Radium-223 Dichloride (Ra-223) in Patients With Castration-Resistant Prostate Cancer (CRPC) and Bone Metastases From the Phase 3 ALSYMPCA Study

Radium-223 dichloride is a first-in-class, α-emitting radiopharmaceutical approved in 37 countries for CRPC patients with bone metastasis. As a high-energy radiation emitter, it induces DNA strand breaks that lead to cell death. It is recommended by the National Comprehensive Cancer Network in the first-line and postdocetaxel settings.[1] More than 90% of metastatic CRPC patients have radiologic evidence of bone metastases, which are a major cause of death and comorbidities; however, most drugs approved for treating bone metastases are limited to palliation or delay of skeletal events.[2,3] In the international phase 3 ALSYMPCA (Alpharadin in Symptomatic Prostate Cancer Patients) trial, radium-223 provided a median OS benefit of 3.6 months compared with placebo, with a robust HR of 0.70 (14.9 months vs 11.3 months; *P*<.001).[4] The time to first symptomatic skeletal event was also significantly delayed by almost half a year (HR, 0.66). Of note, the radium-223 arm yielded an excellent safety profile, with fewer AEs than the placebo arm as well as a low myelosuppression rate.

Although radium-223 has a benign safety profile, patients who receive this agent must be followed over time so that any safety signals, including the development of secondary tumors, can be identified. Dr Sten Nilsson presented an analysis of long-term treatment-related AEs in CRPC patients from the ALSYMPCA trial.[5] Safety data were available for 1.5 years after the final injection. The investigators focused on reports of acute myelogenous leukemia, myelodysplastic syndrome, primary cancers in other organs, and aplastic anemia in primary bone cancer.

The ALSYMPCA trial randomized 921 patients 2:1 to receive the best standard of care plus either radium-223 by injection (50 kBq every 4 weeks) or matching placebo.[4] Patients had confirmed, symptomatic CRPC, at least 2 bone metastases, and no known visceral metastases. Previous treatment with docetaxel was permitted but not required. Patients were stratified based on baseline alkaline phosphatase levels, current bisphosphonate use (yes vs no), and prior docetaxel (yes vs no). After patients received 6 injections, they entered the designated 3-year follow-up program, with examinations occurring every second month for the first 6 months and every fourth month thereafter.

Treatment in the study began in 2008, and the final injection was administered in mid-2011. Patients in the radium-223 arm (n=406) and the control arm (n=168) who entered into long-term follow-up shared similar characteristics, including age, race, and total alkaline phosphatase. Approximately 40% of the patients were receiving bisphosphonates, and nearly 60% had received prior docetaxel. The 2 treatment arms had similar ECOG performance status, pain levels, and extent of disease. Eighty-three percent of the radium-223 group and 71% of the placebo group completed all 6 injections of the study treatment. The median follow-up was longer for patients who received radium-223

ABSTRACT SUMMARY Activity of Abiraterone Acetate in Metastatic Patients With Castration-Resistant Prostate Cancer (mCRPC) Previously Treated With Ketoconazole: A Prospective Phase II Study From the Prostate Cancer Clinical Trials Consortium

Patients who had received prior ketoconazole treatment were excluded from the pivotal phase 3 trials of abiraterone acetate. A prospective phase 2 study was conducted to evaluate the efficacy of abiraterone acetate in metastatic CRPC patients who had received prior ketoconazole (Abstract 53). The 42 enrolled patients received abiraterone (1000 mg daily) plus prednisone (5 mg twice daily). Serum androgen levels, including dehydroepiandrosterone (DHEA), were measured by liquid chromatography followed by mass spectrometry at baseline and during treatment. The limit of quantitation (LOQ) for DHEA was defined as less than 0.250 ng/mL. The median time to PSA progression was 16 weeks (range, 4-64 weeks). Median radiographic PFS was 24 weeks (range, 1-88 weeks). A PSA decline of at least 30% at 12 weeks was observed in 1 patient (11%) with DHEA levels less than the LOQ vs 17 patients (55%) with DHEA levels at or exceeding the LOQ (*P*=.028). Median time to pain progression was 8 weeks (range, 4-32 weeks) for patients with DHEA levels below the LOQ vs 18 weeks (range, 4-64 weeks) for patients with DHEA levels at or exceeding the LOQ (*P*=.012). Patients with DHEA levels at or exceeding the LOQ also showed a significantly improved median radiographic PFS at 12 weeks compared with patients whose DHEA levels were below the LOQ (36 weeks [range, 1-88 weeks] vs 12 weeks [range, 4-64 weeks]; *P*=.0006).

Table 2. Long-Term Treatment-Related AEs in the ALSYMPCA Trial

	Number (%) of Patients With Treatment-Related AEs					
	Radium-223 n=404			Placebo n=167		
Posttreatment Follow-Up AEs	All Grades	Grades 3/4	Grade 5	All Grades	Grades 3/4	Grade 5
Anemia	11 (3)	5 (1)	0	5 (3)	1 (1)	0
Aplastic anemia	1 (<1)	1 (<1)	0	0	0	0
Leukopenia	2 (<1)	2 (<1)	0	0	0	0
Neutropenia	2 (1)	2 (1)	0	0	0	0
Thrombocytopenia	4 (1)	0	0	0	0	0

AEs, adverse events; ALSYMPCA, Alpharadin in Symptomatic Prostate Cancer Patients.
Data from Nilsson S et al. ASCO GU abstract 9. *J Clin Oncol.* 2014;32(4)(suppl).[5]

ABSTRACT SUMMARY Impact of Prior Response to Abiraterone Acetate (AA) on Subsequent Activity of Docetaxel (D) in Metastatic Castration-Resistant Prostate Cancer (mCRPC) Patients (pts)

Establishing optimal sequencing options with docetaxel and abiraterone remains an important area of research in metastatic CRPC. In a recent report, docetaxel showed poor activity in metastatic CRPC patients who failed to demonstrate a PSA decline of at least 50% during prior treatment with abiraterone acetate (Mezynski J et al. *Ann Oncol* 2012;23(11):2943-2947). To further investigate this finding, a study compared outcomes in patients identified in registries at 2 Canadian centers who received docetaxel after abiraterone acetate (Abstract 97). Response to abiraterone was defined as a decrease in PSA of at least 50%. The study included 14 abiraterone responders and 26 nonresponders (including 16 patients who experienced no PSA decline at all). Three-fourths of patients had received docetaxel before abiraterone. In contrast to the findings of Mezynski and colleagues, a similar proportion of patients in each abiraterone response group showed PSA decreases of at least 50% (*P*=.72) or at least 30% (*P*=.75) with docetaxel. The study also revealed a similar median PFS (*P*=.44) and median OS (*P*=.62) with docetaxel in both response groups.

(10.4 months vs 7.6 months) and, consistent with the limited survival of this patient population, only 16 radium-223 patients and 4 placebo patients completed the 3 years of follow-up. The analysis occurred approximately 1.5 years after the last patient's final injection.

Very few treatment-related hematologic AEs were reported (Table 2). Treatment-related AEs were observed in 20 radium-223 patients and 5 placebo patients. In the radium-223 patients, the most common AEs of any grade were hematologic and included anemia (3%), neutropenia (1%), thrombocytopenia (1%), leukopenia (<1%), and aplastic anemia (<1%). Grade 3/4 hematologic AEs included anemia (1%), neutropenia (1%), aplastic anemia (<1%), and leukopenia (<1%). The low rate of myelosuppression suggests that radium-223 might be safely used in combination with other drugs to treat this patient population. Nonhematologic treatment-related AEs were rare in both arms, with isolated AEs occurring in less than 1% of patients in the radium-223 arm. There were no reports of acute myelogenous leukemia, myelodysplastic syndrome, or primary bone cancer. One patient in the radium-223 arm presented with aplastic anemia. This patient had received chemotherapy and repeated external beam radiotherapy for bone metastases. Primary cancer in other organs was identified in 2 patients in the radium-223 arm and 3 patients in the placebo arm, but these cancers were deemed unrelated to the study treatment. Full 3-year follow-up analysis will be presented at the 2014 meeting of the American Society of Clinical Oncology.

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Sipuleucel-T in Metastatic Castration-Resistant Prostate Cancer (mCRPC) Patients ≥80 Years-Old: Data From PROCEED

Sipuleucel-T is an autologous cellular immunotherapy that is approved in the United States and the European Union for the treatment of patients with asymptomatic or minimally symptomatic metastatic CRPC. The patient's peripheral blood mononuclear cells are harvested and treated outside the body with the fusion product of prostatic acid phosphatase and granulocyte-macrophage colony stimulating factor. Patients receive a total of 3 sipuleucel-T infusions at weeks 0, 2, and 4. The procedure was approved following the phase 3 IMPACT (Immunotherapy Prostate Adenocarcinoma Treatment) trial of 512 patients, which demonstrated a 22% reduction in the risk of death relative to placebo.[1] The ongoing phase 4 PROCEED (PROVENGE Registry for the Observation, Collection, and Evaluation of Experience Data) registry trial was mandated by the FDA to evaluate sipuleucel-T in the real-world setting.[2] The primary objective of the trial is to further quantify the risk of cerebrovascular events; the secondary objective is to evaluate OS. Each patient undergoes measurement at weeks 0, 2, and 4 of product parameters such as APC counts, total nucleated cell counts, and APC activation, which reflects product potency.

The high prevalence of metastatic CRPC in older men, as well as their potential for diminished immunologic function, led Dr Chadi Nabhan and colleagues to examine the disease characteristics and sipuleucel-T product parameters in patients who enrolled in PROCEED at ages 80 years or older.[3] As of May 2013, 1376 patients were enrolled and 1274 had completed treatment, including 250 patients (20%) ages 80 years or older. Baseline median PSA levels were higher in older patients compared with those younger than 80 years (21.6 ng/mL vs 14.8 ng/mL). Lower proportions of older patients had an ECOG performance status of 0 (52.8% vs 70.0%), a Gleason score of 8 or higher (33.2% vs 53.7%), and more than 10 bone metastases (13.2% vs 18.7%) compared with patients younger than 80 years.

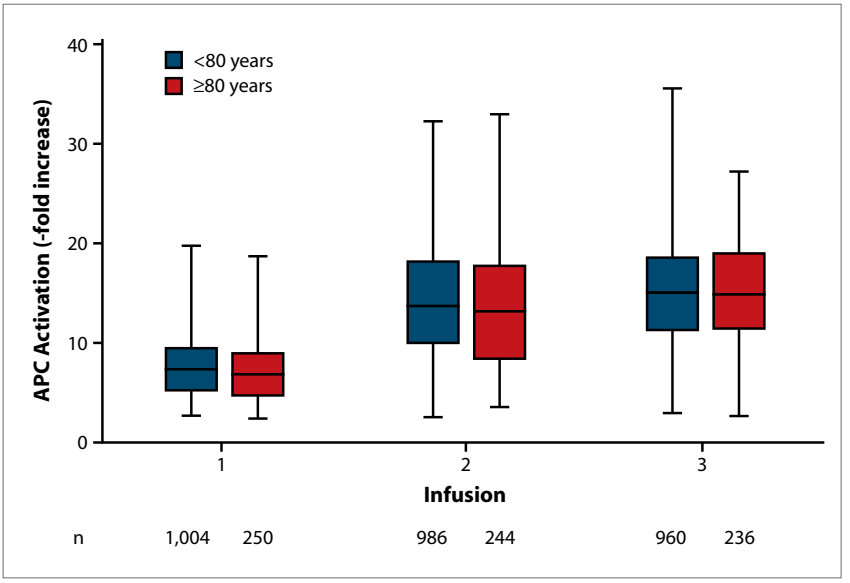

Figure 5. In an analysis of patients receiving sipuleucel-T in the PROCEED registry, the level of APC activation was comparable in older and younger patients.

APC, antigen-presenting cell; PROCEED, PROVENGE Registry for the Observation, Collection, and Evaluation of Experience Data. Adapted from Nabhan C et al. ASCO GU abstract 64. *J Clin Oncol.* 2014;32(4)(suppl).[3]

APC and total nucleated cell counts were maintained at weeks 0, 2, and 4, with a slight decrease from week 0 to week 2; measurements at these time points were similar in both age groups. Sipuleucel-T product parameters were also similar. The level of APC activation was comparable in both age groups, with evidence of immunologic prime boosting (Figure 5). A prior analysis of 3 phase 3 studies showed a significant relationship between cumulative APC activation and OS in metastatic CRPC patients treated with sipuleucel-T (P=.041).[4] Further follow-up will explore correlations between OS and product parameters in both age groups.

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Highlights in Advanced Prostate Cancer From the 2014 American Society of Clinical Oncology Genitourinary Cancers Symposium: Commentary

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Throughout the past several years, the American Society of Clinical Oncology Genitourinary Cancers Symposium has become one of the premier meetings in the field. It is an important stage for presentations of timely, state-of-the-art clinical trial data. At the 2014 symposium, studies in advanced prostate cancer focused on agents such as enzalutamide, orteronel, abiraterone acetate, and sipuleucel-T.

Enzalutamide

The late-breaking abstract session included results of the PREVAIL (A Safety and Efficacy Study of Oral MDV3100 in Chemotherapy-Naive Patients With Progressive Metastatic Prostate Cancer) trial, a pivotal phase 3 study of enzalutamide in men with chemotherapy-naive metastatic prostate cancer.[1] This study is essentially a companion to the AFFIRM (A Multinational Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oral MDV3100 in Patients With Progressive Castration-Resistant Prostate Cancer Previously Treated With Docetaxel-Based Chemotherapy) trial of enzalutamide vs placebo in 1199 prostate cancer patients who were castration-resistant and had progressed on prior docetaxel-based chemotherapy.[2] In that study, enzalutamide demonstrated a clear survival advantage over placebo—a 4.8-month improvement in overall median survival—that resulted in approval by the US Food and Drug Administration (FDA) for that indication. The PREVAIL trial enrolled a larger population of 1700 chemotherapy-naive metastatic castration-resistant prostate cancer patients who were randomized 1-to-1 to enzalutamide or placebo. The trial was powered for both overall survival benefit and radiographic progression-free survival. An interim analysis was performed after 539 deaths. The study demonstrated a statistically significant benefit in enzalutamide over placebo, with a 29% reduction in the risk of death (hazard ratio [HR], 0.7; $P<.0001$), as well as an 81% reduction in the risk of radiographic progression-free survival (HR, 0.19; $P<.0001$). Importantly, the differences in overall survival were seen within the first 6 months—and remained separated all the way through this population of patients who died on study. These results support the early use of enzalutamide in chemotherapy-naive castration-resistant prostate cancer, even in patients with good performance status and minimal symptoms, and suggest that use of this agent should not be delayed until the second-line or third-line setting.

A study from the United Kingdom evaluated the use of enzalutamide after failure of docetaxel and abiraterone in patients with metastatic castration-resistant prostate cancer.[3] This single-center study included 23 patients who had received prior docetaxel and abiraterone; 35% had also received cabazitaxel and 52% had received diethylstilbestrol. In this heavily pretreated population, enzalutamide decreased levels of the prostate-specific antigen (PSA) by at least 50% in 39% of patients. Patients who were sensitive to abiraterone had an increased response to enzalutamide, as measured by a decrease in PSA of more than 50% ($P=.03$ and $r=0.45$), suggesting that patients who respond to abiraterone may benefit from subsequent enzalutamide therapy. A concern in this study was the short duration of these responses, even in patients who were sensitive to abiraterone. Biochemical progression-free survival was 15.7 weeks in patients who had shown previous sensitivity to abiraterone and 11.4 weeks in those who were not sensitive to abiraterone. Although enzalutamide appears to reduce PSA, it is unclear whether the duration of that response will translate into a clinical benefit for the patient population. Based on the PREVAIL data,[1] enzalutamide should be used early and not reserved for patients who have failed abiraterone or docetaxel.

Orteronel

Dr Robert Dreicer presented results of a phase 3 randomized, double-blind multicenter study of orteronel (also known as *TAK-700*) plus prednisone vs prednisone alone in men with metastatic castration-resistant prostate cancer who have progressed follow-

ing docetaxel-based chemotherapy.[4] Orteronel is a nonsteroidal, androgen synthesis inhibitor similar in class to abiraterone acetate. It has shown activity in the phase 1 and phase 2 settings.[5] This study was the first phase 3 trial to evaluate orteronel in the docetaxel-treated patient population. It was powered to identify an overall survival benefit. Nearly 2000 patients were randomized 2-to-1 to receive orteronel plus prednisone or prednisone alone.

The study was halted early because it was failing to meet its primary endpoint; the median overall survival benefit was 17.0 months for the orteronel-plus-prednisone arm and 15.2 months for the prednisone-alone arm, a difference that was not statistically significant (HR, 0.886; *P*=.1898). This study stratified findings according to geographic regions, including North America, Europe, and the rest of the world. More than half of the study population was enrolled in Europe. Among these patients, orteronel was not associated with a significant improvement in overall survival (which was 18.3 months for the orteronel-plus-prednisone arm vs 17.8 months for the prednisone-alone arm). This latter finding is interesting because it exceeds the overall survival observed in the control arms in the AFFIRM (13.6 months) and Cougar 301 (10.9 months) trials and is comparable to the treatment arms in those studies that led to the FDA approvals of enzalutamide and abiraterone, respectively.[2,6] The fact that the survival associated with orteronel in European patients mimics the survival seen with abiraterone and enzalutamide treatment arms suggests that there was a poststudy treatment effect to subsequent therapy, which might have mitigated the overall survival endpoint that the orteronel study was based on. This bias is unfortunate for orteronel because otherwise the agent appears to have clinical activity comparable to other agents approved in this setting. The study endpoint of overall survival was affected by a change in the landscape of treatment options available for patients at this time. To demonstrate a benefit in overall survival, a study would need to be much larger or conducted in areas where those agents are not yet available.

From a toxicity standpoint, orteronel was reasonably tolerated. There were gastrointestinal side effects, including nausea, vomiting, fatigue, and diarrhea, but no significant percentages of grade 3 or higher toxicities.

Radium Dichloride

Dr Sten Nilsson presented data from a 1.5-year posttreatment follow-up analysis of radium dichloride in patients with castration-resistant prostate cancer and bone metastases from the phase 3 ALSYMPCA (A Phase III Study of Alpharadin [Radium-223] in Patients With Symptomatic Hormone Refractory Prostate Cancer With Skeletal Metastases) study.[7,8] The analysis evaluated the long-term follow-up safety outcomes in this pivotal trial, which compared radium to placebo in patients who were previously treated with chemotherapy or considered unfit for chemotherapy. The analysis specifically sought to identify hematologic and nonhematologic toxicities, including any evidence of secondary malignancies or hematologic malignancies (in particular, acute myelogenous leukemia, myelodysplastic syndrome, and anaplastic anemia). There were no significant differences in toxicities between the radium and the placebo groups. Primary cancer in other organs was reported in only 5 patients—2 in the radium group and 3 in the placebo group—and none of these cancers were leukemias. The analysis found no evidence of delayed toxicities, at least in this short interval of 1.5 years. Obviously, it will be important to collect more long-term follow-up data. It appears, however, that radium is safe and without long-term consequences in patients with symptomatic hormone-refractory prostate cancer and skeletal metastases, particularly in consideration of their expected survival.

ABSTRACT SUMMARY Dose-Modified Abiraterone Acetate (AA) in Men With Metastatic Castration Resistant Prostate Cancer (mCRPC): The Princess Margaret Cancer Centre (PM) Experience

In a phase 1 trial of abiraterone acetate, plasma concentrations of the drug were higher when it was administered with a high-fat meal compared with fasting (Attard G et al. *J Clin Oncol*. 2008;26[28]:4563-4571). A study of single-dose pharmacokinetics showed similar maximal plasma drug concentrations of abiraterone following doses of 250 mg or 500 mg in fed patients or 1000 mg in fasting patients. To evaluate the association between abiraterone acetate dosage and patient outcomes, a retrospective review was conducted of 90 men who received full-dose abiraterone (1000 mg) in the fasting state and 21 men who received low-dose abiraterone (250 mg or 500 mg) with food, the latter mostly in the prechemotherapy setting (Abstract 61). No significant differences in outcomes were observed for full-dose vs low-dose patients based on PSA response rate (43% vs 32%; *P*=.4), PFS (4.4 months vs 5.6 months; *P*=.3), and OS (18.7 months vs 16.6 months; *P*=.2). In the subset of chemotherapy-naive men, the 34 patients treated at the full dose showed a nonsignificant trend toward an improved PSA response rate compared with the 16 men who received the low dose (53% vs 27%; *P*=.09); however, the full-dose and low-dose groups showed similar rates of PFS (5.5 months vs 4.6 months; *P*=.9) and OS (18.8 months vs not reached; *P*=.5). The authors concluded that the results support prospective research to investigate the efficacy of low-dose abiraterone acetate in the context of exploring options for resource-limited treatment settings.

Abiraterone Acetate

A phase 2 study from the Prostate Cancer Clinical Trials Consortium examined the activity of abiraterone acetate in metastatic patients with castration-resistant prostate cancer previously treated with ketoconazole.[9] Ketoconazole is a known inhibitor of androgen synthesis; it has a similar mechanism to abiraterone, but it is not as specific or potent.[10] The 42 patients in this study had a median duration of exposure to ketoconazole of approximately 38 weeks, which is a significant exposure time for this agent. PSA levels declined by at least 30% in 48% of patients and by at least 50% in 38% of patients. There were 2 disappointing findings in the study: a short time to progression for PSA of 16 weeks, and a median radiographic progression-free survival of approximately 6 months. Therefore, although abiraterone was clinically active in patients previously treated with ketoconazole, the effect was not durable and showed evidence of overlapping resistance.

An interesting study from the Princess Margaret Cancer Centre was based on the observation that the drug exposure associated with abiraterone acetate varies according to whether the drug is administered in the setting of a high-fat meal or a fasting state.[11] A previous study by Attard and colleagues showed that in patients treated with abiraterone acetate at lower dosages of 250 mg/day or 500 mg/day (as opposed to the standard recommended dosage of 1000 mg/day), drug exposure will increase by up to 4.4-fold when the dose is administered with a high-fat meal.[12] Cost was another factor driving this study; in Canada and other settings, lower dosages of abiraterone acetate may be more cost-effective. In this study, 21 patients received a low dosage in the setting of a high-fat meal and 90 patients received the full dosage while fasting. There was no statistically significant difference in radiographic progression-free survival or PSA response rate between the dosages. A limitation to this study was that it did not appear to include a prespecified statistical analysis. Only 21 patients received the low dosage, so the lack of statistical significance is difficult to interpret because the study was not powered to show it. In addition, the progression-free survival rates of 4.4 months for the full dosage and 5.6 months for the low dosage are approximately half those seen in other clinical trials, such as Cougar-301.[6] The low progression-free survival rates suggest that this endpoint was not sensitive in this study group. I am hesitant to draw any conclusions from this study, based on the limited experience and flawed data set. At this time, I would not prescribe low-dose abiraterone acetate, although this approach is worth studying prospectively.

Dr Rana McCay presented results of a phase 2 study combining abiraterone acetate with a 5α-reductase inhibitor, dutasteride.[13] Preclinical evidence suggests that 5α-reductase activity in the formation of dihydrotestosterone may make tumors relatively resistant to abiraterone acetate.[14] This study aimed to determine whether the addition of an inhibitor to that enzyme might improve overall response. The 40 enrolled patients received initial therapy with abiraterone acetate and prednisone. After 2 months, dutasteride was added, and the regimen was continued until radiographic progression. (It was unclear why the treatments were staggered.)

After 2 months of treatment, the median PSA declined by 54%. The median time to PSA nadir was approximately 3.2 months. The decline in PSA was 50% or greater in 60% of patients and 90% or greater in 30%. The toxicity profiles were similar to those in previous studies of abiraterone. The most common side effects were fatigue, hypertension, and hypokalemia. Only 4% of patients experienced grade 3 or higher adverse events. The authors stated that "Our nonrandomized trial precludes a definite conclusion about the combination." In my view, the PSA response rate of 54% does not support an additional clinical activity of dutasteride. The data do suggest that there is no negative signal to dutasteride, so it is reasonable to add abiraterone in patients already receiving dutasteride. However, this study does not suggest to me that dutasteride should be added to treatment in patients already receiving abiraterone.

Docetaxel

Another Canadian study evaluated registries at 2 centers to determine whether patients' response to docetaxel corresponded to whether they had responded to previous treatment with abiraterone acetate.[15] Response to abiraterone, defined as an associated decline in PSA of 50% or more, was identified in 14 of 40 patients. After treatment with docetaxel, there were no significant differences between the abiraterone responders and nonresponders in PSA response rates, median progression-free survival, or overall survival. A limitation to this study was the limited number of patients in the abiraterone acetate–responders group. The overall median survival was 48.1 weeks in patients who had responded to abiraterone acetate and 38.6 weeks in patients who had not responded to it. This outcome is low for docetaxel, suggesting that prognosis will be poor in patients who receive previous treatment with abiraterone acetate, regardless of whether they respond to it. The most important conclusion from this study is that the more patients are treated with secondary hormonal therapies, the less they will respond to or survive after subsequent treatment with docetaxel chemotherapy. More aggressive or effective chemotherapies may be needed in this setting.

IRX4204

Dr Fairooz Kabbinavar presented results of an open-label, phase 2 study of the pan-retinoid X receptor (RXR) agonist IRX4204 in taxane-resistant, castration-resistant metastatic prostate cancer.[16]

This study was based on preclinical work showing that IRX4204 is a potent small-molecule inhibitor of the RXR receptor; in preclinical studies, IRX4204 synergizes with insulin-like growth factor–binding protein to induce apoptosis in prostate cancer.[17] An earlier phase 1 study enrolled only 1 prostate patient, but this patient demonstrated a decline in PSA of more than 90% that lasted more than 7 months.[18] This phase 2 study included patients with metastatic castration-resistant prostate cancer in the chemorefractory setting. Treatment benefit was defined as a decline in PSA of 50% or more, a partial or complete response of measurable disease as assessed by the Response Evaluation Criteria In Solid Tumors (RECIST), or progression-free survival lasting more than 56 days. Among the 23 patients in the study, 13 (57%) exhibited a treatment benefit. All of these patients achieved a progression-free survival of more than 56 days. Only 3 of the 13 patients had a 50% decline in PSA. No patients had an objective response. IRX4204 was well tolerated. It was associated with some increases in triglycerides, as might be expected, and decreases in thyroid-stimulating hormone. The outcomes in this study, however, did not demonstrate any clinical activity that warrants further development of IRX4204 in prostate cancer at this time.

Sipuleucel-T

PROCEED (PROVENGE Registry for Observation, Collection, and Evaluation of Experience Data) is a large, prospective national registry of patients receiving sipuleucel-T that is focused primarily on safety issues. Approximately 1250 patients in the registry completed treatment with a standard regimen of sipuleucel-T.[19] An analysis of PROCEED data evaluated whether prior therapy with abiraterone or enzalutamide affected the production of sipuleucel-T in patients.[20] The study found no such effect, suggesting that prior or concomitant treatment with enzalutamide or abiraterone is not a detriment to producing the sipuleucel-T agent. These results support the overlapping use of these hormonal treatments with sipuleucel-T in clinical practice.

The PROCEED registry enrolled 278 patients older than 80 years.[19] An analysis presented by Dr Chadi Nabhan aimed to identify any differences in antigen-presenting cell activation between older and younger patients.[21] The analysis found no difference, which demonstrates that there is adequate immune upregulation in elderly patients. The extent to which the immune upregulation that occurs ex vivo translates into in vivo activation is unknown, but data from the phase 3 IMPACT (Immunotherapy Prostate Adenocarcinoma Treatment) trial suggest that older patients benefit from sipuleucel-T as much as younger patients do.[22] The results of this analysis suggest that it is feasible to administer sipuleucel-T on a large national scale and in a broad spectrum of patients, including those older than 80 years.

The IMPACT trial led to the approval of sipuleucel-T in the United States for treatment of asymptomatic or minimally symptomatic metastatic castration-resistant disease.[22] Dr Charles Drake presented results of a post hoc analysis of data from the IMPACT trial, which examined antigen spread and survival with sipuleucel-T in advanced prostate cancer.[23] The analysis evaluated serum from 93 patients who received sipuleucel-T and 40 control patients. The immunoglobulin G (IgG) responses were tested against an array of secondary antigens, including PSA. Antigen production in the patients who had received sipuleucel-T was significantly greater as compared with those in the control group. Among the patients who received sipuleucel-T, overall survival was longer in those who achieved IgG responses to at least 2 secondary antigens compared to those who did not respond (HR, <0.4). This study suggests that the type of broader immune activation that may occur in the setting of a prostatic acid phosphatase (PAP) and GM-CSF stimulation may be an important indicator of the clinical benefit to sipuleucel-T. It is possible that the mechanism of sipuleucel-T immune activation extends beyond PAP protein activation. This analysis provides the important insight that targeted immune treatments can have greater effects in vivo than might otherwise be predicted, which may be why sipuleucel-T has activity across a broad range of patients and populations.

Dr Steven Finkelstein and colleagues analyzed data from PROCEED to evaluate the impact of prior radiation therapy on sipuleucel-T product parameters.[19,24] In PROCEED, 112 patients (9%) had received palliative radiation to bone metastases before undergoing treatment with sipuleucel-T. There were 517 patients (42%) who had not received prior radiation (to the prostate or any other site). Patients who had not received prior radiation were compared with those who had received palliative radiation. To balance the cohorts, the study was narrowed to patients who had undergone prior prostatectomies, and later relapsed. This criterion eliminated from the analysis patients who presented with widely metastatic disease (and consequently would not have undergone prostatectomy). There were 44 patients who had undergone prostatectomy and then went on to receive palliative radiation and 159 patients who had undergone prior prostatectomy but had not received radiation. These well-balanced populations showed equal abilities to create the vaccine. The mean cumulative antigen-presenting cell counts were similar between the groups. The patients who had not received radiation had a slightly higher total neutrophil count. There was a slight difference in antigen-presenting cell activation; the patients who had received prior radiation had an antigen-presenting cell count of 34.2 vs 38.5 in patients who had not received prior radiation (P=.048).

The study authors concluded that there was no evidence showing that prior

radiation inhibited successful production of sipuleucel-T. A concerning observation in this study was the difference in the amount of antigen-presenting cell activation—specifically, the activation rate was approximately 10% lower in the patients who had received prior radiation. Although this difference may not be clinically significant, it would be ideal to use an agent such as sipuleucel-T earlier in the setting of castration-resistant prostate cancer, before the need for palliative radiation therapy, especially to the bones (where it may affect the marrow and the release of antigen-presenting cells). The effect on antigen-presenting cell activation in these patients appears to be relatively minor and limited, however, so prior radiation should not be a contraindication to using sipuleucel-T.

Acknowledgment

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Notes

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

BRIEF SUMMARY – See full Prescribing Information for complete product information

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

DOSAGE AND ADMINISTRATION

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

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

CONTRAINDICATIONS: None.

WARNINGS AND PRECAUTIONS

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

Table 1 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. PROVENGE [package insert]. Dendreon Corporation; June 2011.
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Dendreon on call
1-877-336-3736

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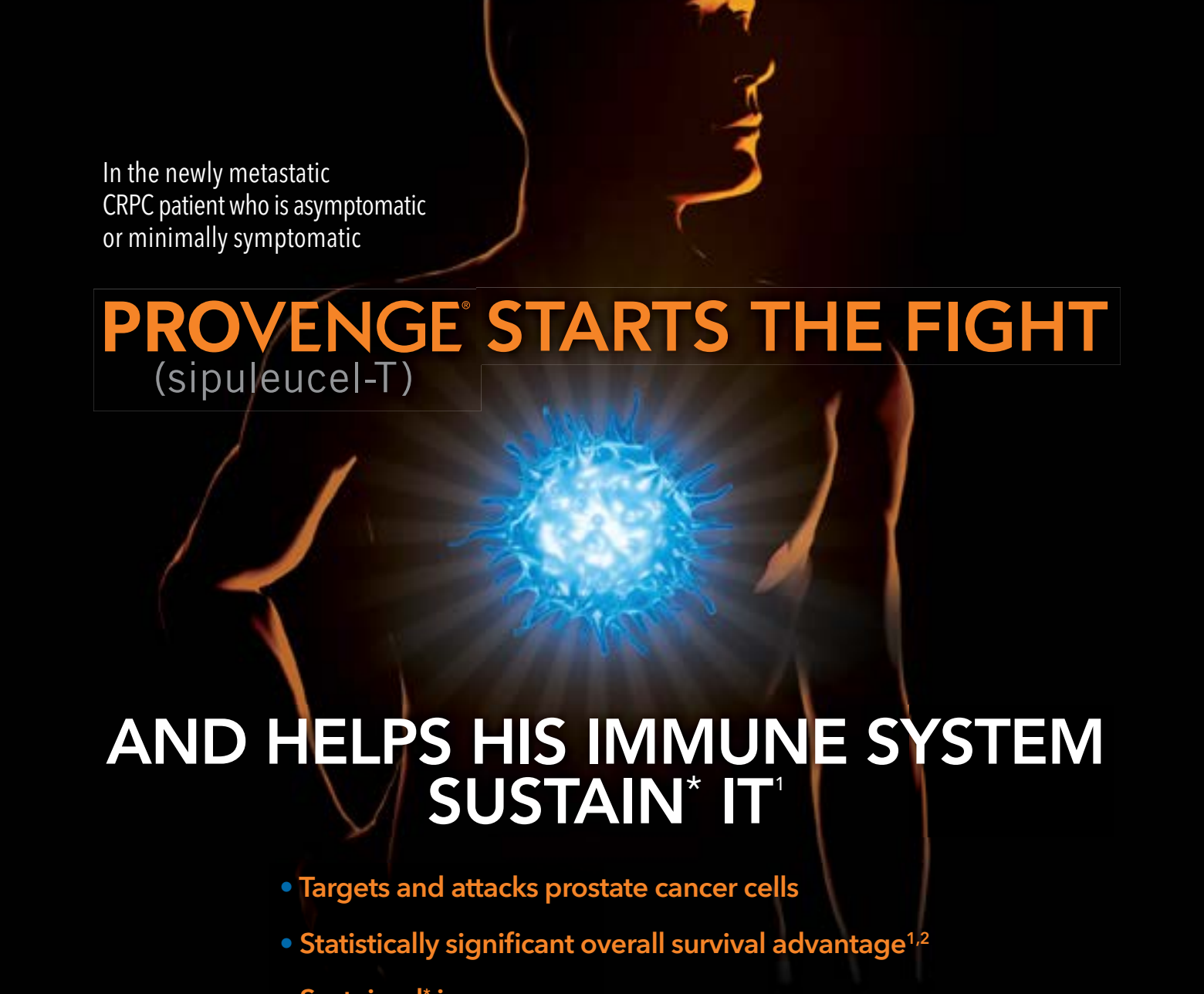
PROVENGE®
(sipuleucel-T)



In the newly metastatic CRPC patient who is asymptomatic or minimally symptomatic

PROVENGE® STARTS THE FIGHT

(sipuleucel-T)

AND HELPS HIS IMMUNE SYSTEM SUSTAIN* IT[1]

- Targets and attacks prostate cancer cells
- Statistically significant overall survival advantage[1,2]
- Sustained* immune response

*A sustained immune response was seen out to 26 weeks in the pivotal study (the last time point measured).[1]

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 pages.

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