Clinical Advances in
HEMATOLOGY & ONCOLOGY™
A Peer-Reviewed Journal

September 2014 Volume 12, Issue 9, Supplement 17

Highlights in Advanced Prostate Cancer From the 2014 AUA and ASCO Meetings

A Review of Selected Presentations From the 2014 American Urological Association Meeting, May 16-21, 2014, Orlando, Florida and the 2014 American Society of Clinical Oncology Meeting, May 30-June 3, 2014, Chicago, Illinois

With Expert Commentary by:
Daniel J. George, MD
Associate Professor of Medicine and Surgery
Divisions of Medical Oncology and Urology
Duke University Medical Center
Durham, North Carolina

ON THE WEB:
www.clinicaladvances.com

Indexed through the National Library of Medicine
(PubMed/Medline), PubMed Central (PMC), and EMBASE

Immunotherapy

Sipuleucel-T–Induced Antigen Spread: Immune Response to Prostate-Specific Antigen Correlates With Improved Overall Survival

A study presented at the 2014 American Urological Association (AUA) meeting reported on the association between a patient's immune system response to sipuleucel-T and his subsequent clinical outcome.[1] The investigators noted that previous studies have demonstrated the importance of the type of immune response generated and survival outcomes in patients receiving sipuleucel-T. In a previous analysis of 3 phase 3 trials of sipuleucel-T, several immune parameters were significantly associated with overall survival (OS): the cumulative antigen-presenting cell activation, the number of antigen-presenting cells, and the total nucleated cell numbers (P<.05 for each).[2] In the same analysis, antigen-specific immune responses, which were detected in 79% of assessed patients, were significantly associated with OS (P=.003).

The current analysis evaluated the effect of antigen spread on outcomes in patients treated with sipuleucel-T. Antigen spread refers to the development of immune responses against antigens other than the primary antigen, which, in the case of sipuleucel-T, is prostatic acid phosphatase. Immune responses may be induced against these secondary antigens if the initial antitumor immune response successfully targets and kills tumor cells, releasing new antigens. These new antigens may then be processed and presented by antigen-presenting cells, potentially activating a new tumor-specific immune response.

Dr Simon J. Hall and his colleagues analyzed data from the double-blind, placebo-controlled, multicenter, phase 3 IMPACT (Immunotherapy Prostate Adenocarcinoma Treatment) trial[3] to evaluate whether sipuleucel-T induces immune responses against secondary prostate tumor antigens and, if so, whether these responses are associated with improved OS.[1] The analysis included 142 patients in the sipuleucel-T arm and 62 patients in the control arm.

The study showed that sipuleucel-T appeared to induce antigen spread. Immunoglobulin G (IgG) immune responses were detected against several known secondary prostate tumor antigens in patients treated with sipuleucel-T. IgG responses were defined as a 2-fold elevation in the serum

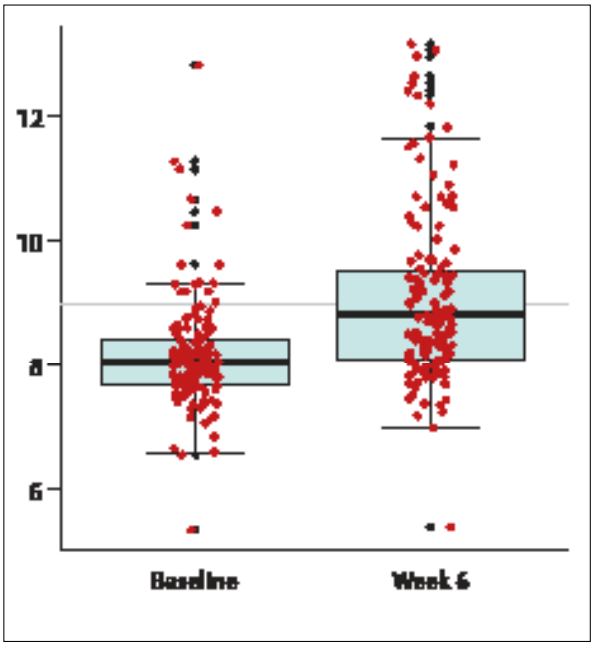


Figure 1. In an analysis of the phase 3 IMPACT trial, IgG responses were observed against the prostate-specific antigen in 25% of patients receiving sipuleucel-T vs 0% of patients in the control group.

IgG, immunoglobulin G; IMPACT, Immunotherapy Prostate Adenocarcinoma Treatment. Adapted from Hall SJ et al. Paper presented at: American Urological Association Annual Meeting; May 16-21, 2014; Orlando, Florida. AUA abstract 14-1585.[1]

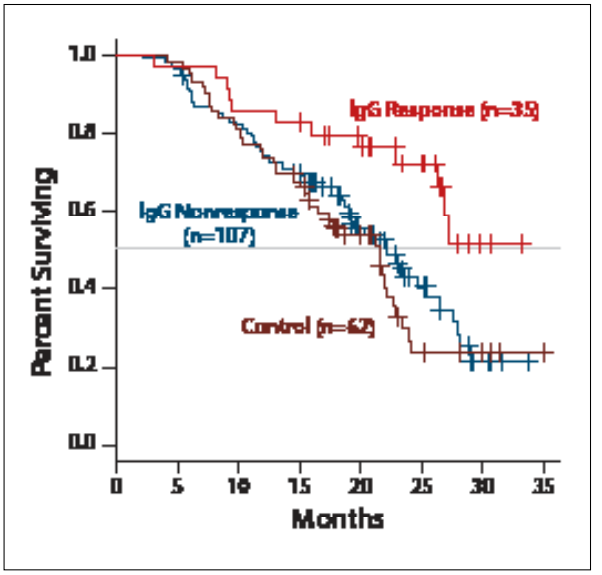


Figure 2. Week 6 IgG responses against several secondary antigens were significantly associated with superior overall survival outcomes in the IMPACT trial.

IgG, immunoglobulin G; IMPACT, Immunotherapy Prostate Adenocarcinoma Treatment. Adapted from Hall SJ et al. Paper presented at: American Urological Association Annual Meeting; May 16-21, 2014; Orlando, Florida. AUA abstract 14-1585. [1]

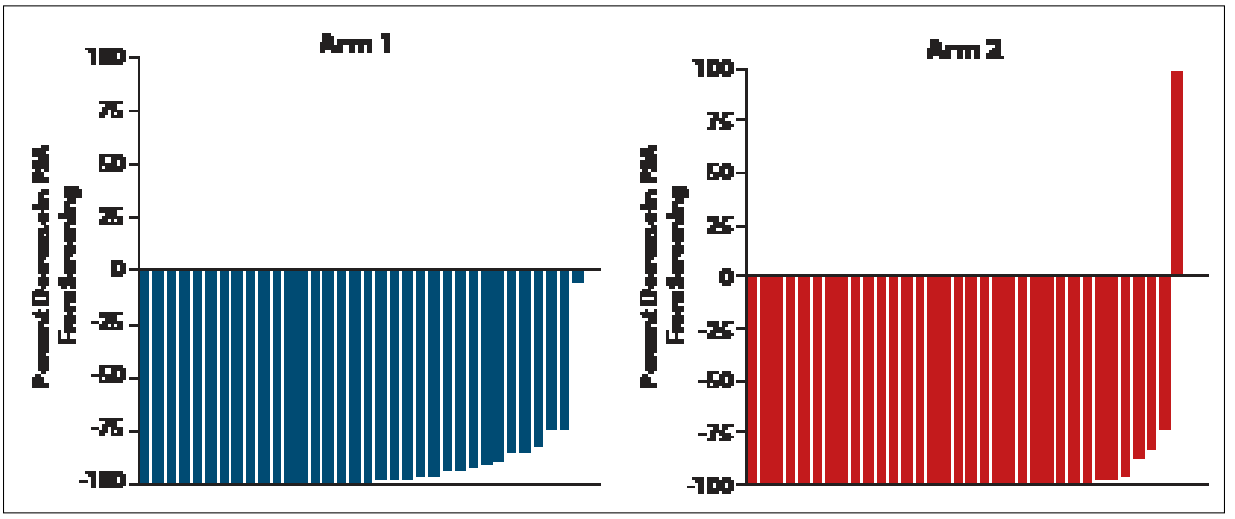


Figure 3. The percentage change in prostate-specific antigen levels from baseline in arm 1, sipuleucel-T followed by ADT, vs arm 2, ADT followed by sipuleucel-T, in a randomized, phase 2 trial.

ADT, androgen-deprivation therapy. Adapted from Antonarakis ES et al. ASCO abstract 5041. *J Clin Oncol*. 2014;32(5 suppl).[5]

IgG level compared with baseline. They were observed against the prostate-specific antigen (PSA) in 25% of patients receiving sipuleucel-T vs 0% of patients in the control group (Figure 1), against the prostate-specific membrane antigen (PSMA) in 21% and 3% of patients, respectively, and against KLK2 in 37% and 3% of patients, respectively. Moreover, week 6 IgG responses against several secondary antigens were significantly associated with superior OS outcomes in the IMPACT trial (Figure 2). The development of immune responses to PSA was associated with a 67% reduction in the risk of death in the sipuleucel-T group vs the control group (hazard ratio [HR], 0.33; 95% CI, 0.17-0.68; *P*<.01). Moreover, among patients who received sipuleucel-T, the risk of death was 58% lower in patients who developed a PSA-specific immune response compared with patients who did not (HR, 0.42; 95% CI, 0.22-0.79; *P*<.01). The investigators concluded that these findings may help identify biomarkers that predict clinical outcomes after treatment with sipuleucel-T.

A Randomized Phase 2 Study Evaluating Optimal Sequencing of Sipuleucel-T (Sip-T) and Androgen Deprivation Therapy (ADT) in Biochemically Recurrent Prostate Cancer

Biochemically recurrent prostate cancer occurs when primary therapy is followed by an increase in PSA levels. Androgen-deprivation therapy (ADT) is commonly used in patients with biochemical recurrence who are at high risk of developing metastases. In addition to its androgen-depriving effects, ADT has also demonstrated immune effects, including induction of antitumor immunity[4] and enhancement of other cancer immunotherapy.

Biochemical recurrence has been proposed as an appropriate setting for evaluating direct immune-based therapies, given that patients with biochemical recurrence tend to have a low disease burden and minimal immune tolerance. Sipuleucel-T is an autologous cellular immunotherapy currently approved for certain patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC). The optimal sequencing of ADT and sipuleucel-T has not been identified.

At the 2014 American Society of Clinical Oncology (ASCO) meeting, Dr Emmanuel S. Antonarakis and colleagues reported results from a randomized phase 2 study evaluating the optimal sequencing of sipuleucel-T and ADT in patients with biochemically recurrent prostate cancer.[5] The study enrolled 68 patients with biochemically recurrent prostate cancer, a serum testosterone level of 200 ng/mL or higher, a PSA doubling time of 12 months or less, and no radiographic evidence of metastases. Patients were randomly assigned to receive sipuleucel-T followed by ADT, which was started 2 weeks after the final sipuleucel-T treatment (34 patients), or ADT followed by sipuleucel-T, which was started after 3 months of an ADT lead-in period (34 patients). In both arms, patients received 3 infusions of sipuleucel-T and 12 months of ADT, administered as two 45-mg subcutaneous leuprolide depot injections at 6-month intervals.

The main objective of the study was to compare immune responses between the arms. The investigators reported similar sipuleucel-T–mediated immune activation whether ADT or sipuleucel-T was administered first, suggesting that sequencing of the 2 therapies does not affect sipuleucel-T immune effects. Antigen-specific T-cell responses, which were evaluated using the interferon-γ Enzyme-Linked ImmunoSpot (ELISPOT) assay and

proliferation assays, were greater in patients receiving sipuleucel-T first than in patients receiving ADT first. The difference was statistically significant starting at week 2.

In both treatment groups, a majority achieved PSA levels that were 5% or less than those measured at baseline (Figure 3). Levels of serum interferon-γ were higher in patients receiving ADT first than in patients receiving sipuleucel-T first. However, the findings regarding enhanced antigen-specific immune activation in patients receiving sipuleucel-T first indicate that this approach may improve the ability of ADT to enhance T-cell effector activity.

The investigators noted that the combination of sipuleucel-T and ADT was well tolerated. They concluded that a combination approach, in which ADT is started after immunotherapy, would enhance T-cell immune responses in patients with biochemically recurrent prostate cancer.

Time to Chemotherapy Following Treatment With Sipuleucel-T: Data From PROCEED

The ongoing, multicenter, phase 4 registry PROCEED (PROVENGE Registry for Observation, Collection, and Evaluation of Experience Data) is enrolling patients receiving sipuleucel-T outside a clinical trial, including patients receiving treatment in community and academic oncology and urology practices. Patients are being monitored for development of serious adverse events (in particular, cerebrovascular events), OS, and the use of other treatments after sipuleucel-T.

At ASCO 2014, Dr Christopher M Pieczonka and colleagues presented results from an analysis of the PROCEED cohort that focused on the time to first subsequent therapy after sipuleucel-T treatment.[6] As of the current analysis, the registry included 1901 patients who had received at least 1 infusion of sipuleucel-T.[7] The median age of sipuleucel-T–treated patients was 72 years; 20% of the patients were at least 80 years old. Nearly all patients were white (87%) or African American (12%), and the median body mass index (BMI) was 28.8 kg/m^2. The mean and median PSA levels were 71.7 ng/mL and 14.9 ng/mL, respectively. The median alkaline phosphatase was 83.0 U/L, the median lactate dehydrogenase was 186.5 U/L, and the median hemoglobin was 12.8 g/dL.

In the current analysis, 1227 patients (65%) had received a subsequent anticancer intervention after sipuleucel-T; this treatment included chemotherapy in 476 patients (25%). The most common interventions were abiraterone, enzalutamide, prednisone, external beam radiation therapy to bone metastases, and denosumab. The most common chemotherapeutic agents were docetaxel, cabazitaxel, and carboplatin.

To assess the relationship between baseline prognostic factors and time to first subsequent anticancer intervention, the investigators performed a stepwise selection method using a Cox regression model. All continuous variables aside from bone metastases were dichotomized at the median value.

In this preliminary statistical modeling of time to first anticancer intervention, the median time to next therapy was 5.7 months, with an interquartile ratio of 3.0 months to 11.9 months. Baseline variables that were significantly and independently associated with a shorter time to first anticancer intervention in the stepwise model were higher baseline alkaline phosphatase value (HR, 1.33; 95% CI, 1.17-1.52; *P*<.001), younger age (HR, 0.86; 95% CI, 0.76-0.98; *P*=.019), higher body weight (HR, 1.14; 95% CI, 1.01-1.30; *P*=.039), and higher baseline PSA (HR, 1.14; 95% CI, 1.01-1.30; *P*=.042).

The median time to chemotherapy was 1.50 months (interquartile range, 7.3 months to not reached). Significant baseline variables independently associated with time to chemotherapy largely overlapped with those associated with time to first intervention. These variables included younger age (HR, 0.70; 95% CI, 0.57-0.86; *P*<.001), higher baseline PSA (HR, 1.47; 95% CI, 1.19-1.81; *P*<.001), higher alkaline phosphatase level (HR, 1.52; 95% CI, 1.24-1.88; *P*<.001), and use of previous chemotherapy (HR, 1.34; 95% CI, 1.05-1.72; *P*=.02).

The investigators noted that the median time to first anticancer intervention was significantly shorter at oncology practices than in urology practices (4.8 months vs 7.3 months; HR, 1.61; *P*<.001). However, because practice type is associated with other baseline variables, it was omitted as a possible predictive factor.

Treatment Practice Patterns in Metastatic Castration-Resistant Prostate Cancer (mCRPC) Patients Prior to Receiving Sipuleucel-T: Data From PROCEED

Another analysis from the PROCEED registry was presented at AUA 2014. It examined treatment practice patterns in men with mCRPC before they received sipuleucel-T.[8] Among the 1974 patients enrolled in PROCEED as of March 2014, baseline PSA data were available for 1883. Oncologists were providing treatment for 65.5% of patients, and urologists were treating the remainder. This trend, however, appears to be changing, as the proportion of patients receiving sipuleucel-T through urology practices has increased over time.

The median age of enrolled patients was 73 years in urology practices and 71 years in oncology practices. Differences in treatment practice patterns emerged based on the PSA level and patient age. Among younger patients (<65 years), the proportion of patients with a baseline PSA below the median was higher in oncology practices than in urology

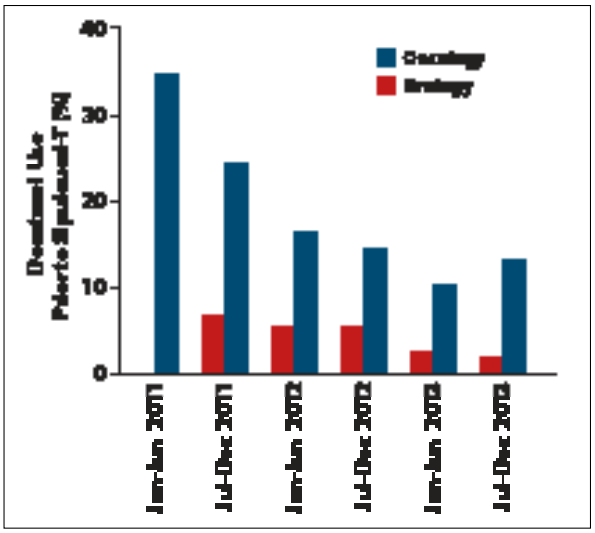


Figure 4. Patients treated in oncology practices were more likely than patients in urology practices to have received prior docetaxel.

Adapted from Cooperberg M et al. Paper presented at: American Urological Association Annual Meeting; May 16-21, 2014; Orlando, Florida. Abstract 14-444.[8]

practices (27% vs 21%). Conversely, among older patients (≥80 years), a higher proportion of those with low baseline PSA received sipuleucel-T from a urology practice than an oncology practice (20% vs 14%). There were also differences in demographics between the practices. There was a higher percentage of African American patients in urology practices than in oncology practices (15% vs 10%). Moreover, the proportion of African American patients with baseline PSA values above the median was higher in urology practices than in oncology practices (19% vs 12.5%).

In general, patients receiving care in oncology practices had a higher baseline PSA value than patients receiving care in urology practices (median PSA of 15.7 ng/mL vs 13.6 ng/mL). There was a trend toward decreasing baseline median PSA levels over time during the registry period. The investigators noted that the median PSA level among all patients in the PROCEED registry (15.0 ng/mL) is lower than the median PSA level among patients enrolled in the IMPACT trial (51.7 ng/mL).[3]

Approximately 74% to 81% of patients had previously received local therapy, and 98% to 99% had previously received hormonal therapy, with similar rates seen across practice type and PSA category. Patients receiving care in oncology practices were more likely to have received prior docetaxel than patients receiving care in urology practices (Figure 4). The proportion of patients with prior docetaxel was higher both in patients with a baseline PSA of 15 ng/mL or less (12.7% vs 2.1%) and patients with a baseline PSA exceeding 15 ng/mL (16.8% vs 5.1%). However, the proportion of patients previously treated with docetaxel generally declined in both practice settings during the registry period.

Use of bone-directed agents was also higher in oncology practices than in urology practices, with higher proportions of patients receiving zoledronic acid (4.8% vs 0.9%) or denosumab (5.6% vs 3.6%). Patients treated in oncology practices were also more likely than patients in urology practices to have received prior enzalutamide (Figure 4). This trend was seen regardless of baseline PSA (≤15 ng/mL, 5.1% in oncology practices vs 2.7% in urology practices; >15 ng/mL, 6.8% vs 2.6%, respectively).

The investigators concluded that the PROCEED registry will continue to provide important information about real-world experience with immunotherapy in patients with prostate cancer receiving care in urology and oncology practices.

A Randomized Phase 2, Open-Label Study of Sipuleucel-T With Concurrent or Sequential Enzalutamide in Metastatic Castration-Resistant Prostate Cancer (mCRPC)

There is a rationale for combining sipuleucel-T and enzalutamide, as the agents are not likely to cross-react, and it has been proposed that androgen receptor (AR)-targeting therapy may enhance the efficacy of cancer vaccines.[9] Moreover, sipuleucel-T and enzalutamide are both commercially available and approved for use in certain patients with mCRPC. However, the optimal timing of each agent has not been determined. The randomized, open-label, phase 2 STRIDE trial (P12-2) was undertaken to evaluate the efficacy and safety of sipuleucel-T and enzalutamide administered concurrently or sequentially. Details of the trial were published as an abstract in conjunction with ASCO 2014.[10] The study enrolled 22 patients with asymptomatic or minimally symptomatic mCRPC who were randomly assigned to concurrent therapy, consisting of enzalutamide at 160 mg once daily that was started 2 weeks prior to sipuleucel-T and continued for 52 weeks, or sequential therapy, in which enzalutamide at 160 mg once daily was started 10 weeks after the initiation of sipuleucel-T. The primary study endpoint was the immune response to PA2024; time to PSA recurrence was an exploratory endpoint. At the time of the analysis, 6 patients (3 patients in each arm) had completed sipuleucel-T treatment (3 infusions). Antigen-presenting cell activation was similar in both arms, with a median cumulative CD54 upregulation of 35.3 with concurrent therapy and 26.6 with sequential therapy. There were CD54-positive cell counts of 1.9×10^9 with concurrent therapy vs 1.8×10^9 cells with sequential therapy. Increased antigen-presenting cell activation was observed at the second sipuleucel-T infusion compared with the

first infusion, indicating an immunologic prime boost. Pre- and postculture cellular compositions were also similar between the arms. The investigators concluded that sipuleucel-T can be administered with concurrent enzalutamide without compromising its potency.

A Randomized, Double-Blind Phase 2 Study of Sipuleucel-T Followed by Indoximod or Placebo in the Treatment of Patients With Asymptomatic or Minimally Symptomatic Metastatic Castration-Resistant Prostate Cancer

Tumor-mediated immune suppression presents a major challenge to the development of effective cancer vaccines. Specifically, the activation of regulatory T cells that inhibit immune responses has been identified as an obstacle to cancer immunotherapy. Although sipuleucel-T may counteract this issue by sensitizing immune cells ex vivo, tumor-mediated immunosuppression could still occur, limiting the antitumor immune response. Indoximod is a compound that inhibits indoleamine 2,3-dioxygenase (IDO), an enzyme that has been implicated in the development of peripheral immune tolerance by promoting the conversion of naive T cells to regulatory T cells. By inhibiting IDO activity, indoximod may reduce immune tolerance. At ASCO 2014, Dr Gautam Jha and Dr Jeffrey Miller presented the study details of an ongoing randomized, double-blind, phase 2 study[11] evaluating whether the addition of indoximod to sipuleucel-T therapy will enhance the immune response and improve clinical outcomes.[12] The study was initiated in October 2012 and plans to enroll 50 patients with mCRPC. Eligible patients have an Eastern Cooperative Oncology Group (ECOG) performance score of 0 to 1, have not received opiates for cancer pain, are not immunosuppressed, and do not have any autoimmune disease. In the study, patients will receive sipuleucel-T therapy and will be randomly assigned to receive oral indoximod or placebo, each administered twice daily, starting after the last sipuleucel-T infusion and continuing for 24 weeks or until disease progression or unacceptable toxicity. The primary objective of the study is to demonstrate augmentation of the immune response to PA2024 at week 14 of therapy. Secondary objectives include safety, pharmacokinetics, efficacy parameters (OS, progression-free survival [PFS], relative response, circulating tumor cells [CTCs], and quality of life). The immune monitoring will include assessments of regulatory T cells, natural killer cells, myeloid-derived suppressor cells, and macrophages. Immune responses to PA2024 will be assessed through ELISPOT, enzyme-linked immunosorbent assay (ELISA), and CD54 upregulation. The IDO inhibitor will be assessed using the kynurenine to tryptophan ratio, as IDO degrades tryptophan. Patients will have the option to undergo paired biopsies to assess tissue immune responses. The investigators noted that this proof-of-principle study could identify a well-tolerated, active option that may warrant testing in larger studies. The estimated date for completion of enrollment is September 2015. The planned completion of correlative studies is January 2016, and planned completion of follow-up is May 2016.

A Phase II Randomized, Open Label Study of Sipuleucel-T Versus Sipuleucel-T and Tasquinimod in Patients With Metastatic Castrate-Resistant Prostate Cancer (CRPC)

The investigational agent tasquinimod targets S100A9, an inflammatory protein that is associated with tumor suppressive myeloid cells. In a randomized, double-blind, placebo-controlled, phase 2 trial, single-agent tasquinimod demonstrated clinical activity in patients with mCRPC.[13] In studies conducted in a mouse prostate cancer model, the addition of tasquinimod to a tumor vaccine was associated with enhanced antitumor effects.[14] Based on this preclinical rationale, a randomized, open-label, phase 2 study was initiated to evaluate sipuleucel-T with or without tasquinimod in patients with mCRPC. Study details were presented as a Trial in Progress abstract at ASCO 2014.[15] The study will randomly assign 60 patients to sipuleucel-T with or without tasquinimod. The primary endpoint, change from baseline in immune response against PA2024 as measured using an ELISPOT assay, will be assessed throughout the treatment period, at weeks 0, 2, 6, 26, and 52. Periodic assessments of safety and immune responses will also be conducted. Secondary endpoints include PFS and OS. The investigators also plan to conduct correlative studies evaluating the immune response and effects of tasquinimod as well as factors associated with clinical efficacy.

Next-Generation Androgen-Deprivation Therapy

Primary, Secondary, and Quality-of-Life Endpoint Results From PREVAIL, a Phase 3 Study of Enzalutamide in Men With Metastatic Castration Resistant Prostate Cancer (mCRPC)

The AR inhibitor enzalutamide inhibits the binding of androgens to the AR, reduces nuclear translocation of the AR, and inhibits DNA binding mediated by the AR.[16] Enzalutamide is approved by the US Food and Drug Administration (FDA) for the treatment of patients with mCRPC previously treated with docetaxel. The approval of enzalutamide in this patient population was based on results from the double-blind, placebo-controlled, 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, which showed a median OS of 18.4 months with enzalutamide vs 13.6 months with placebo (HR, 0.63; 95% CI, 0.53-0.75; $P<.001$).[17] Enzalutamide was also associated with a significant improvement over placebo in secondary endpoints, including median radiographic progression-free survival (rPFS; 8.3 vs 2.9 months; HR, 0.40; $P<.001$).[17]

The randomized, phase 3 PREVAIL (A Safety and Efficacy Study of Oral MDV3100 in Chemotherapy-Naive Patients With Progressive Metastatic Prostate Cancer) trial evaluated the efficacy and safety of enzalutamide in patients not previously treated with chemotherapy. Results of the PREVAIL trial were presented at ASCO 2014 by Dr Andrew J. Armstrong.[18] The trial enrolled men with metastatic prostate cancer that was progressing despite the use of androgen-deprivation therapy (ADT). Patients were chemotherapy-naive, could be asymptomatic or mildly symptomatic, and could have received steroids. All patients had a baseline Brief Pain Inventory (BPI) score of 4 or lower.

A total of 1717 patients were randomly assigned to enzalutamide at 160 mg/day (872 patients) or placebo (842 patients). ADT was maintained in all patients. The co–primary endpoints were OS and rPFS. At an interim analysis conducted after 540 deaths had occurred, an independent data monitoring committee recommended halting the PREVAIL trial based on a statistically significant benefit seen with enzalutamide, which showed superior outcomes as assessed by both co–primary endpoints. The trial was therefore unblinded and patients in the placebo arm were offered enzalutamide.

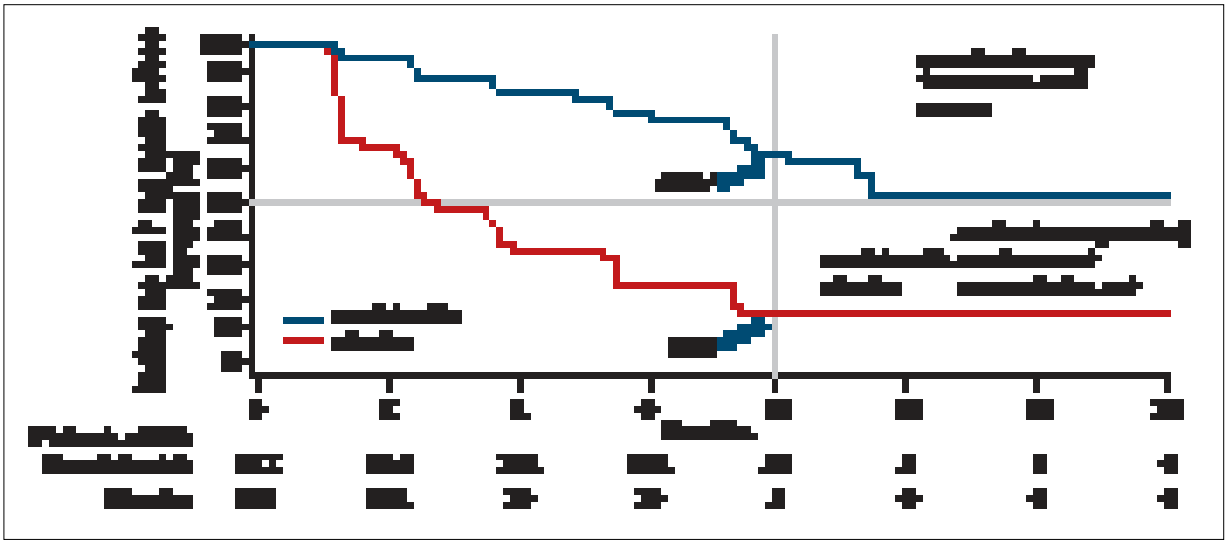


Figure 5. In the PREVAIL trial, enzalutamide was significantly more effective than placebo as assessed by rPFS after a median follow-up of 22 months.

*Percentage of patients free from rPFS at 12 months. NYR, not yet reached; PREVAIL, A Safety and Efficacy Study of Oral MDV3100 in Chemotherapy-Naive Patients With Progressive Metastatic Prostate Cancer; rPFS, radiographic progression-free survival. Adapted from Armstrong AJ et al. ASCO abstract 5007. *J Clin Oncol*. 2014;32(5 suppl).[18]

Dr Armstrong presented results from the time of the unblinding. He noted that baseline characteristics were well balanced between the arms. The median age of enrolled patients was approximately 72 years (range, 42-93 years), approximately 77% of patients were white, and approximately half had a Gleason score of 8 or less at the initial diagnosis.

The majority of patients (68%) had an ECOG performance status of 0. More than 85% of patients had received at least 1 prior antiandrogen agent. Although patients with significant baseline pain were excluded, Dr Armstrong noted that the disease appeared to affect quality of life; the median baseline Functional Assessment of Cancer Therapy–Prostate (FACT-P) score was 121 to 122 out of a range of 0 (worst) to 156 (best). Established prognostic factors, including lactate dehydrogenase, alkaline phosphatase, and hemoglobin levels, were well balanced between the arms. Bone metastases were present in the majority of patients at baseline, with approximately 32% of patients having 10 or more at screening. Visceral disease in the liver and/or lung was present in approximately 12% of patients.

After a median follow-up of 22 months, enzalutamide was significantly more effective than placebo as assessed by rPFS, with a median rPFS not reached in the enzalutamide arm vs 3.9 months in the placebo arm (HR, 0.186; 95% CI, 0.15-0.23; *P*<.0001; Figure 5). The proportion of patients alive and free from radiographic progression at 12 months was 65% with enzalutamide and 14% with placebo.

Enzalutamide was also associated with a significant improvement in OS. The median OS was 32.4 months with enzalutamide and 30.2 months with placebo (HR, 0.706; 95% CI, 0.60-0.84; *P*<.0001), representing a 29% reduction in the risk of death. The 12-month survival rates with enzalutamide and placebo were 82% and 73%, respectively. An updated OS analysis conducted after an additional 4 months of follow-up confirmed the survival benefit of enzalutamide, with the median OS not reached in the enzalutamide arm vs 31.0 months in the placebo arm (HR, 0.73; 95% CI, 0.63-0.85; *P*<.001).

The median duration of treatment was substantially longer with enzalutamide than placebo, at 16.6 months and 4.6 months, respectively. More than two-thirds of patients in the enzalutamide arm (68%) received at least 12 months of therapy compared with 18% of patients in the placebo arm. Patients in the enzalutamide arm were also less likely than patients in the placebo arm to use subsequent therapies; 40% and 70% of patients, respectively, used at least 1 subsequent life-extending therapy. The most commonly used subsequent therapies were docetaxel and abiraterone.

Dr Armstrong noted that there were differences in subsequent therapy use based on geographic location, which he attributed to differences in the availability of abiraterone worldwide. Enzalutamide was associated with a 17-month delay in the time to chemotherapy vs placebo, with the median time to chemotherapy of 28.0 months with enzalutamide and 10.8 months with placebo (HR, 0.349; 95% CI, 0.30-0.40; *P*<.0001).

Enzalutamide was also associated with a high PSA response rate. A confirmed PSA decline of at least 50% was reported in 78.0% of the enzalutamide arm and 3.5% in the placebo arm (*P*<.0001); a decline of at least 90% was reported in 46.8% and 1.2%, respectively (*P*<.0001). The median time to PSA progression was 11.2 months with enzalutamide and 2.8 months with placebo (HR, 0.169; 95% CI, 0.15-0.20; *P*<.0001). Among patients with measurable soft tissue disease at baseline, the objective response rate was 58.8% with enzalutamide (including 19.7% complete responses), compared with 4.9% with placebo (*P*<.0001).

The risk of skeletal-related events was reduced by 28% with enzalutamide; the median time to first skeletal-related event, defined as the time to first radiation therapy or surgery to bone for prostate cancer, pathologic bone fracture, spinal cord compression, or change in therapy to treat bone pain, was 31.1 months with enzalutamide and 31.3 months with placebo (HR, 0.718; 95% CI, 0.61-0.84; *P*<.0001). The 1-year event rates were 84% and 73%, respectively.

Quality-of-life analyses using the FACT-P scale revealed significantly greater improvements with enzalutamide vs placebo in all tested quality-of-life domains, including physical, social/family, emotional, and functional well being. Future analyses will investigate the specific quality-of-life attributes that were improved with enzalutamide.

In the safety analysis, the primary all-grade adverse events observed at an increased rate with enzalutamide vs placebo were fatigue (35.6% vs 25.8%), hot flushes (18.0% vs 7.7%), and hypertension (13.4% vs 4.1%). The most common grade 3 or higher adverse events were hypertension (6.8% vs 2.3%) and falls (1.4% vs 0.7%). Enzalutamide was not associated with higher rates of grade 3 or higher cardiac adverse events or alanine aminotransferase (ALT) elevations. Seizures were reported in 1 patient in each arm.

Dr Armstrong concluded that enzalutamide, available as an oral, once-daily medication with good tolerability, was associated with delayed radiographic progression, reduced risk of death, delayed time to chemotherapy, and improved quality of life. Overall, enzalutamide was associated with a meaningful clinical benefit in this population of patients with mCRPC receiving ADT.

Enzalutamide (ENZA) in Combination With Abiraterone Acetate (AA) in Bone Metastatic Castration Resistant Prostate Cancer (mCRPC)

Adaptive androgen signaling has been identified as a driver of metastatic progression in CRPC.[19] Previous studies have shown that several newer agents that target

androgen signaling are associated with a feedback loop. The androgen biosynthesis inhibitor abiraterone depletes androgen levels in the circulation and the tumor microenvironment but leads to increased AR expression.[19] The AR antagonist enzalutamide inhibits nuclear localization of AR but is associated with a concomitant increase in androgen concentrations.[20] It has been proposed that the combination of enzalutamide and abiraterone acetate may inhibit these feedback mechanisms that may contribute to resistance and thereby enhance therapeutic efficacy.

To test this hypothesis, a clinical trial was undertaken evaluating the combination of enzalutamide and abiraterone acetate in patients with mCRPC with bone metastases. Results of the study were presented at ASCO 2014 by Dr Eleni Efstathiou.[21] A total of 60 patients received enzalutamide at 160 mg once daily, abiraterone acetate at 1 g once daily, and prednisone at 5 mg twice daily. Patients underwent blood collection, bone marrow biopsies, and aspirate collection at baseline and week 9.

Most patients were white (85%), and the median age was 66 years (range, 40-82 years). Patients had received a median of 1 prior hormonal treatment (range, 1-4). Forty percent of patients had received a prior antiandrogen agent, 13% had received prior chemotherapy, 8% had received prior estrogens or prednisone, and 10% had received other therapies. The median PSA at baseline was 20.7 ng/dL (range, 1-670 ng/dL), and 67% of evaluable patients had a Gleason score of 8 or higher. Approximately half of patients had more than 20 bone metastases, and 28% had lymph nodes larger than 2 cm. At baseline, visceral metastases were detected in 8% of patients, and bone marrow infiltration was present in 32% of patients.

The adverse event profile of the combination was similar to that reported with each independent agent in prior reports. The most frequently reported adverse events of any grade, independent of cause, were fatigue (73%), hyperglycemia (65%), hot flushes (43%), nausea (23%), hypertension (22%), hypomagnesemia (18%), and headache (17%). Elevations in aspartate aminotransferase (AST) and ALT were observed in 37% and 28% of patients, respectively. There were no grade 4 or 5 adverse events. The most common grade 3 adverse events were hypertension (13%), increase in alanine aminotransferase (10%), increase in alkaline phosphatase (7%), and arthralgia (5%). Three patients (5%) discontinued treatment owing to adverse events.

An assessment of drug-drug interactions between the 2 agents showed that enzalutamide reduced the concentration of abiraterone by 23%, which was considered below the threshold of clinical relevance. Similarly, abiraterone had no clinically relevant effect on the trough concentration of enzalutamide, which was similar to that reported in the AFFIRM trial.[22]

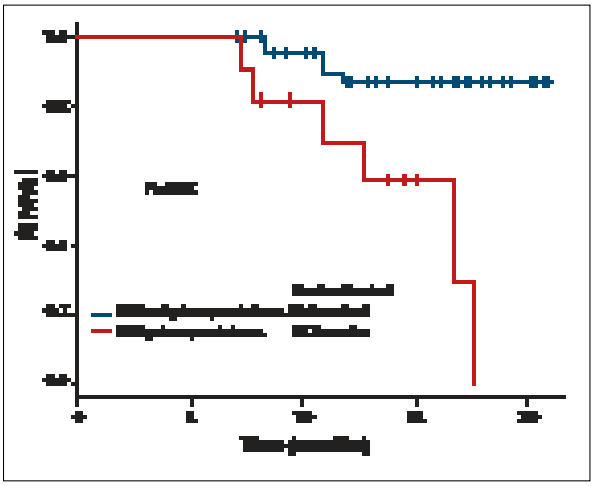


Figure 6. In a trial evaluating the combination of enzalutamide and abiraterone acetate in patients with mCRPC with bone metastases, survival was significantly shorter in patients with primary resistance vs those without primary resistance.

mCRPC, metastatic castration-resistant prostate cancer. Adapted from Efstathiou E et al. ASCO abstract 5000. *J Clin Oncol.* 2014;32(5 suppl).[21]

A pharmacodynamics analysis showed that the combination of enzalutamide and abiraterone was associated with substantial reductions in androgen levels. By week 9, levels of testosterone and androstenedione declined to undetectable levels in the blood and bone marrow in 80% of patients. Analysis of paired tissue specimens in patients with a PSA decline showed a reduction in nuclear localization of AR and the downstream mediator NKX3.1 by week 9.

Primary resistance, defined as overt clinical and/or radiologic disease progression after the start of treatment, occurred in 20% of patients. The patients discontinued treatment within approximately 4 months. Survival was significantly shorter in patients with primary resistance vs those without primary resistance, with a median OS of 16.7 months vs not reached, respectively (P=.0002; Figure 6).

Substantial PSA declines were observed in the majority of patients receiving enzalutamide and abiraterone. PSA declines of at least 50% and at least 90% were observed in 78% and 50% of patients, respectively, and 13% of patients had a PSA of 0.1 ng/mL or less. In an exploratory analysis, primary resistance was significantly associated with a lack of PSA decline (P=.008).

A post hoc analysis of prespecified clinical characteristics revealed that prior treatment with chemotherapy was associated with a higher risk of primary resistance. Small patient numbers precluded statistical analysis of other factors.

Dr Efstathiou also discussed the relevance of AR gene alterations on the development of primary resistance to abiraterone and enzalutamide. AR gene rearrangement has been identified as a mechanism of resistance to AR-

targeted therapy, as some gene rearrangements create AR splice variants that are constitutively active and lack the C-terminal AR ligand-binding domain, thus promoting resistance to AR-targeted therapy.[23]

Previous studies from patients receiving either abiraterone or enzalutamide have suggested an association with molecular biomarkers, including AR alterations, and responses to therapy. Pretreatment expression of N-terminal AR and the presence of CYP17 are associated with a benefit from both abiraterone and enzalutamide.[19,20] Moreover, expression of a truncated form of AR, called *AR splice variant-7* (AR-V7), is associated with resistance to enzalutamide.[24]

The significance of AR-V7 in the development of resistance to AR-targeted therapies was further evaluated in another abstract at ASCO,[25] discussed later in this report. Although AR-V7 is an important AR splice variant, multiple other variants have also been identified. Therefore, to more broadly account for AR variants that may affect responses to abiraterone and enzalutamide, the investigators analyzed the ratio of C-terminal (ligand-binding domain) to N-terminal (transcriptional-activating domain) AR expression. Confirming the importance of other variants, Dr Efstathiou referred to tissue samples from 2 patients with high N-terminal AR expression and low C-terminal AR expression, only 1 of whom was AR-V7–positive.

In conclusion, the combination of enzalutamide and abiraterone was associated with no unexpected adverse reactions or clinically relevant drug-drug interactions. Dr Efstathiou commented that the adaptive responses that had been observed with the individual agents were not observed with the combination strategy. Although the majority of patients had substantial PSA declines, approximately 20% of patients had primary resistance and discontinued therapy within a short period of time. The C-terminal:N-terminal ratio of AR expression appeared to significantly predict whether patients with mCRPC will benefit from androgen-signaling inhibitors.

Main Oncologic Endpoints of the TROG 03.04 (RADAR) Trial for Men With Locally Advanced Prostate Cancer

It is well established that the addition of adjuvant androgen suppression (AS) to radiotherapy improves outcomes in patients with castrate-sensitive, locally advanced prostate cancer.[26,27] The optimal duration of AS in this setting remains unclear. A treatment period of 28 to 36 months has demonstrated superiority over a substantially shorter period of 3 to 8 months.[28] However, long-term adjuvant AS is associated with a higher risk of adverse events.[29]

The randomized Trans-Tasman Radiation Oncology Group (TROG) trial 96.01 demonstrated that 6 months of neoadjuvant ADT in combination with radiotherapy is associated with a significant reduction in the risk of distant progression (HR, 0.49; 95% CI, 0.31-0.76; *P*=.001), prostate cancer–specific mortality (HR, 0.49; 95% CI, 0.32-0.74; *P*=.0008), and all-cause mortality (HR, 0.63; 95% CI, 0.48-0.83; *P*=.0008) compared with radiotherapy alone.[30]

To further evaluate the optimal use of adjuvant AS, the TROG investigators undertook TROG 03.04, also called the *RADAR* (Randomised Androgen Deprivation and Radiotherapy) trial. Results were presented at ASCO 2014 by Dr James William Denham.[31] The RADAR trial compared an AS treatment duration of 18 months vs 6 months and also evaluated the benefit of adding zoledronic acid, which had previously demonstrated efficacy in metastatic CRPC.[32] To evaluate both variables, the investigators used a 2 × 2 factorial design, comparing 4 treatment strategies: 6 months of AS with or without zoledronic acid, and 18 months of AS with or without zoledronic acid. The AS regimen consisted of intramuscular leuprorelin at 22.5 mg administered every 3 months and zoledronic acid administered intravenously at 4 mg every 3 months. After 5 months, all patients received 7 weeks of radiotherapy. The primary endpoint was prostate cancer–specific mortality.

The trial was open to patients with stage T2 to T4, N0, M0 prostate cancer with a good performance status. Between 2003 and 2007, a total of 1071 men enrolled at 23 centers across Australia and New Zealand. The median age of enrolled patients was 68 years, and patients were followed for a median of 7.4 years.

After a median follow-up of 7.4 years, the 18-month AS plus zoledronic acid regimen was significantly more effective than the 6-month AS regimen without zoledronic acid as assessed by the risk of PSA progression (HR, 0.71; 95% CI, 0.53-0.95; *P*=.02) and the need for a secondary therapeutic intervention (HR, 0.67; 95% CI, 0.48-0.95; *P*=.02). In contrast, among the patients receiving 6 months of AS, outcomes were worse among patients also receiving zoledronic acid, who had a shorter time to PSA progression. Dr Denham noted that this qualitative interaction necessitated a comparison of all 4 treatment arms in pairwise analyses, rather than grouping the arms to evaluate each treatment variable. This approach lowered the statistical power of the trial.

An evaluation of outcomes according to baseline Gleason score found that the benefit of the longer treatment period plus zoledronic acid was observed only in patients with a score of 8 to 10. In these patients, 18 months of AS plus zoledronic acid was more effective than 6 months of AS without zoledronic acid, providing a nearly 40% reduction in the risk of PSA progression (HR, 0.59; 95% CI, 0.37-0.94; *P*=.03) and a 45% reduction in the risk of distant progression (HR, 0.54; 95% CI, 0.29-1.00; *P*=.048).

In patients with lower Gleason scores (≤7), a longer AS treatment duration showed benefit, whereas the addition of zoledronic acid did not. Among patients not receiving zoledronic acid, the longer AS regimen was beneficial, demonstrating a 35% reduction in the risk of PSA progression compared with 6 months of AS (HR, 0.65; 95% CI, 0.43-0.98; *P*=.04). Regardless of the AS treatment duration, the addition of zoledronic acid was associated with worse outcomes. Among patients receiving 6 months of AS, there was a trend toward a higher risk of distant progression in those who also received zoledronic acid (HR, 1.75; 95% CI, 0.96-3.19; *P*=.07).

Further investigation found that the higher risk of progression associated with zoledronic acid was attributed to an increased incidence of bone metastatic progression. Among patients receiving 6 months of AS, those also receiving zoledronic acid were 85% more likely than those not receiving zoledronic acid to develop bone progression (HR, 1.85; 95% CI, 1.11-3.10; *P*=.02). This effect was further pronounced among patients with a Gleason score of 7 or less. Dr Denham noted that in absolute values, the risk of bone progression was low, at less than 1% per year.

In an analysis of all endpoint outcomes (PSA progression, bone progression, distant progression, and secondary treatment intervention), extending the duration of AS therapy from 6 months to 18 months appeared to provide little benefit in patients with a Gleason score higher than 7. However, in this patient population, the addition of zoledronic acid was associated with improvements in all endpoints, with the best outcomes observed in patients receiving 18 months of AS plus zoledronic acid. Conversely, in patients with a Gleason score of 7 or less, extending the duration of AS therapy from 6 months to 18 months appeared beneficial as assessed by multiple endpoints, but the addition of zoledronic acid was not beneficial and may have increased the risk of bone metastases.

To reconcile these disparate outcomes, Dr Denham hypothesized that the effect of zoledronic acid on tumor cells varies based on the Gleason score. Zoledronic acid may effectively kill tumor cells in patients with a high Gleason score but may have a protective effect against the bone marrow microdeposits present in patients with a low Gleason score. Dr Denham noted that bone metastases are increased in the context of testosterone recovery that occurs with AS and zoledronic acid.

Longer AS duration and the addition of zoledronic acid did not increase treatment-related morbidity, such as rectal or urinary toxicity beyond 18 months postrandomization or adverse quality-of-life effects beyond 3 years. In the first 3 years, there was an increased risk of nonvertebral fractures in patients receiving 18 months of AS, but the incidence of vertebral fractures was not increased. Two cases of osteonecrosis of the jaw were reported.

Dr Denham noted that additional follow-up was needed to further clarify the role of the longer AS duration, to assess the degree of benefit associated with 18 months of AS plus zoledronic acid, and to evaluate factors affecting the risk of soft tissue metastases. The 10-year data will be evaluable in 2017.

Phase 3, Randomized, Placebo-Controlled Trial of Orteronel (TAK-700) Plus Prednisone in Patients (pts) With Chemotherapy-Naïve Metastatic Castration-Resistant Prostate Cancer (mCRPC) (ELM-PC 4 trial)

Orteronel is an investigational nonsteroidal agent that inhibits androgen biosynthesis by selectively inhibiting 17,20-lyase, an enzyme involved in androgen synthesis that is upregulated in mCRPC. After a phase 1/2 study demonstrated the safety of orteronel and antitumor activity in mCRPC,[33] several phase 3 trials were initiated to evaluate the efficacy and safety of orteronel in various patient populations.

At the 2014 ASCO Genitourinary Cancers Symposium, Dr Robert Dreicer presented results from the ELM-PC 5 (Evaluation of the Lyase Inhibitor Orteronel in Metastatic Prostate Cancer 5) trial, a randomized, double-blind, placebo-controlled, phase 3 trial of orteronel plus prednisone in patients with mCRPC that had progressed during or after docetaxel-based chemotherapy.[34] In this trial, orteronel was associated with improvements in rPFS but not OS in the overall population. In the subset of patients from areas other than Europe or North America, orteronel was associated with an improvement in OS.

At ASCO 2014, Dr Ronald De Wit presented results from ELM-PC 4, a randomized, placebo-controlled, phase 3 study comparing orteronel plus prednisone vs prednisone alone in patients with mCRPC not previously treated with chemotherapy.[35] The trial enrolled 1560 patients with asymptomatic or mildly symptomatic, chemotherapy-naive mCRPC not requiring opioids at screening. Patients were randomly assigned to orteronel at 400 mg (781 patients) or placebo (779 patients), each administered twice daily in combination with prednisone 5 mg twice daily. Patients were enrolled between October 2010 and June 2012 from 324 study centers located across 6 continents and were stratified based on geographic region (Europe [54%], North America [22%], or other [24%]) and presence of radiographic disease progression at screening.

The co–primary endpoints of the study were rPFS and OS. The study was initially designed based on a 90% power to detect a difference in OS and an rPFS of greater than 90%. However, the changing treatment landscape for prostate cancer and the increasing availability of alternate therapies—including abiraterone and enzalutamide, which were approved during the enrollment period—prompted

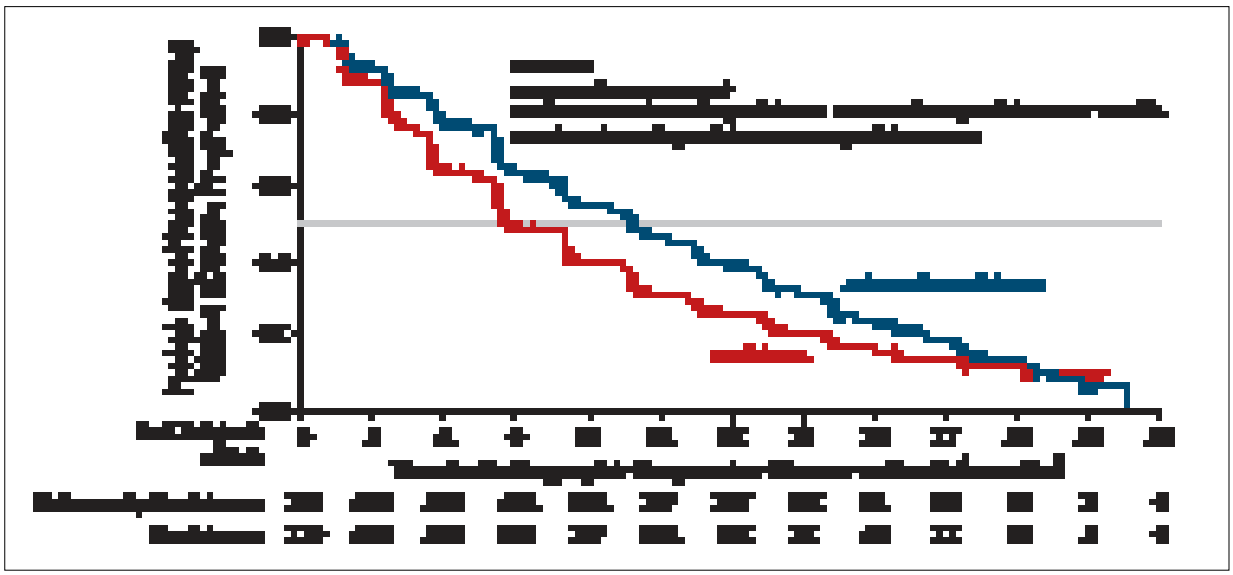


Figure 7. At the final overall survival analysis of the ELM-PC 4 trial, the median rPFS was 13.8 months with orteronel and 8.7 months with placebo.

ELM-PC 4, Evaluation of the Lyase Inhibitor Orteronel in Metastatic Prostate Cancer; rPFS, radiographic progression-free survival. Adapted from De Wit R et al. ASCO abstract 5008. *J Clin Oncol.* 2014;32(5 suppl).[35]

investigators to amend the protocol to conduct the final analysis after fewer deaths, yielding lower statistical power.

Baseline characteristics were well balanced between the arms. The median PSA was approximately 55 ng/mL in both arms. Approximately half of all patients had a Gleason score of 8 or higher, and approximately a quarter of all patients had a hemoglobin level of 12 g/dL or less. Visceral disease was present in 17% of the combination arm and 18% of the control arm, and radiographic disease progression was present in 51% of patients in each arm.

At the interim analysis, orteronel plus prednisone was associated with a significant improvement in rPFS over prednisone alone, with a median rPFS of 11.0 months and 8.3 months, respectively (HR, 0.70; 95% CI, 0.5-0.8; *P*<.001). This finding was confirmed at a subsequent assessment conducted at the final OS analysis, at which point the median rPFS was 13.8 months with orteronel and 8.7 months with placebo (HR, 0.71; 95% CI, 0.63-0.80; *P*<.00001; Figure 7). However, the study did not meet its primary endpoint of OS, demonstrating no significant difference in median OS with orteronel vs placebo (31.4 months vs 29.5 months; HR, 0.92; 95% CI, 0.79-1.08). Subgroup analyses did not show a trend toward greater benefit with orteronel in any subgroup, including the subset of patients living outside Europe or North America, in whom the use of subsequent newer therapies (eg, abiraterone, enzalutamide) was less common.

In regard to secondary efficacy endpoints, orteronel was more effective than placebo in several outcomes, including PSA50 response at 12 weeks (50% vs 28%; *P*<.0001), CTC conversion at 12 weeks (40% vs 25%; *P*<.001), median time to docetaxel (23 months vs 19 months; *P*=.007), and median time to any subsequent therapy (17.2 months vs 13.9 months; *P*<.001). Dr De Wit noted that median testosterone levels declined substantially in both treatment arms by week 12 and remained low through week 24.

Treatment discontinuations were common, with 28% of patients in the orteronel arm and 26% of patients in the placebo arm receiving treatment for less than 20 weeks. The most common reasons for discontinuing orteronel plus prednisone were adverse events (26%) and disease progression (21%). The most common reasons for discontinuing placebo plus prednisone were disease progression (31%) and adverse events (15%).

Clinical adverse events occurring more frequently with orteronel vs placebo included nausea (36% vs 15%), fatigue (34% vs 20%), constipation (33% vs 15%), and diarrhea (28% vs 14%). Laboratory adverse events occurring at higher rates with orteronel vs placebo included increased lipase (24% vs 4%), increased amylase (19% vs 3%), increased ALT (6% vs 1%), and increased AST (5% vs 2%). However, laboratory adverse events did not generally translate into clinical events, as only 2% of patients receiving orteronel developed pancreatitis (vs 0% in the control arm). The most frequent grade 3 or higher adverse events reported with orteronel were increased lipase (17%) and increased amylase (10%).

Chemotherapy

Impact on Overall Survival (OS) With Chemohormonal Therapy Versus Hormonal Therapy for Hormone-Sensitive Newly Metastatic Prostate Cancer (mPrCa): an ECOG-Led Phase III Randomized Trial

ADT has been the standard of care for hormone-sensitive metastatic prostate cancer for decades. For patients with mCRPC, docetaxel was the first agent to provide a survival benefit. However, the optimal use of chemotherapy in the context of ADT is unclear.

Although most prostate cancers are initially responsive to ADT, tumors often overcome androgen suppression. The use of early chemotherapy plus ADT has been proposed as a strategy for lengthening the duration of remission, as testosterone-independent clones would be attacked early. Another potential benefit of this approach would be that chemotherapy is started earlier in the course of management, before some patients become too frail for it. Several potential drawbacks have been noted for early chemotherapy plus ADT. It has been proposed that ADT may alter cell cycle progression, making cells less responsive to cytotoxic agents.

The randomized, phase 3 CHAARTED (Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer) trial (ECOG 3805) was designed to evaluate whether adding docetaxel at the time of starting ADT would extend OS in patients with hormone-naive metastatic prostate cancer. Results of the trial were presented at ASCO 2014 by Dr Christopher J Sweeney.[36]

A total of 790 docetaxel-naive patients were randomly assigned to receive ADT with or without docetaxel (75 mg/m^2 every 21 days for up to 6 cycles). Patients were stratified based on multiple relevant baseline and treatment characteristics, including extent of metastases, age, ECOG performance status, use of combined androgen blockade, planned use of preventive agents for skeletal-related events, and prior adjuvant ADT.

Patient and disease characteristics were well balanced between the arms. Patients' median age was 63 to 64 years. In both arms, most patients were white (89% in the docetaxel arm and 87% in the control arm). Patients had an ECOG performance score of 0 (70%) or 1 (30%). Approximately two-thirds of patients had a high volume of metastases, and more than two-thirds had a Gleason score of 8 to 10 (67% in the docetaxel arm vs 70% in the control arm). The median PSA at the time of ADT initiation was 56.0 ng/mL in the docetaxel arm and 50.5 ng/mL in the control arm. Nearly 75% of patients in each arm had received no localized treatment, and nearly 20% had undergone prior prostatectomy. A small proportion of patients (4%-5%) had previously received adjuvant ADT.

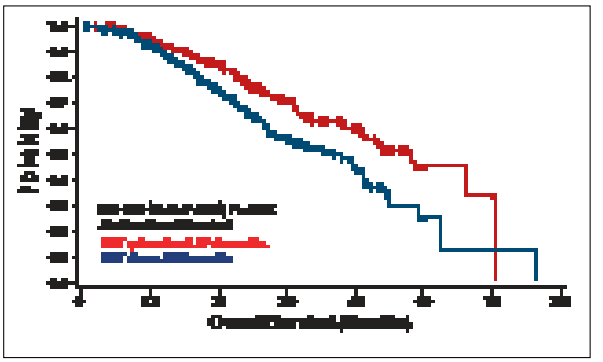


Figure 8. In the phase 3 CHAARTED trial, the addition of docetaxel to ADT was associated with a significant improvement in survival after a median follow-up of 29 months.

ADT, androgen-deprivation therapy; CHAARTED, Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer. Adapted from Sweeney C et al. ASCO abstract LBA2. *J Clin Oncol.* 2014;32(5 suppl).[36]

After a median follow-up of 29 months, the addition of docetaxel to ADT was associated with a significant improvement in survival, with a median OS of 57.6 months vs 44.0 months with ADT alone (HR, 0.61; 95% CI, 0.47-0.80; *P*=.0003; Figure 8). Approximately 83% of deaths in each arm were attributed to prostate cancer.

The survival benefit with docetaxel was primarily observed in the subgroup of patients with a high volume of metastases. Among these patients, the median OS was 49.2 months with ADT plus docetaxel vs 32.2 months with ADT alone (HR, 0.60; 95% CI, 0.45-0.81; *P*=.0006). Conversely, in the subset of patients with a low volume of metastatic disease, the median OS was not reached in either arm, and there was no significant difference between the arms (HR, 0.63; 95% CI, 0.34-1.17; *P*=.14). The addition of docetaxel to ADT appeared to be beneficial across patient subgroups, although these subset analyses did not reach statistical significance owing to small patient numbers.

Docetaxel plus ADT was significantly more effective than ADT alone as assessed by multiple secondary endpoints, including the proportion of patients with a PSA level of less than 0.2 ng/mL at 6 months (27.5% vs 14.0%; *P*<.0001), the proportion of patients with a PSA level of less than 0.2 ng/mL at 12 months (22.7% vs 11.7%; *P*<.0001), the median time to CRPC (20.7 months vs 14.7 months; HR, 0.56; 95% CI, 0.44-0.70; *P*<.0001), and the median

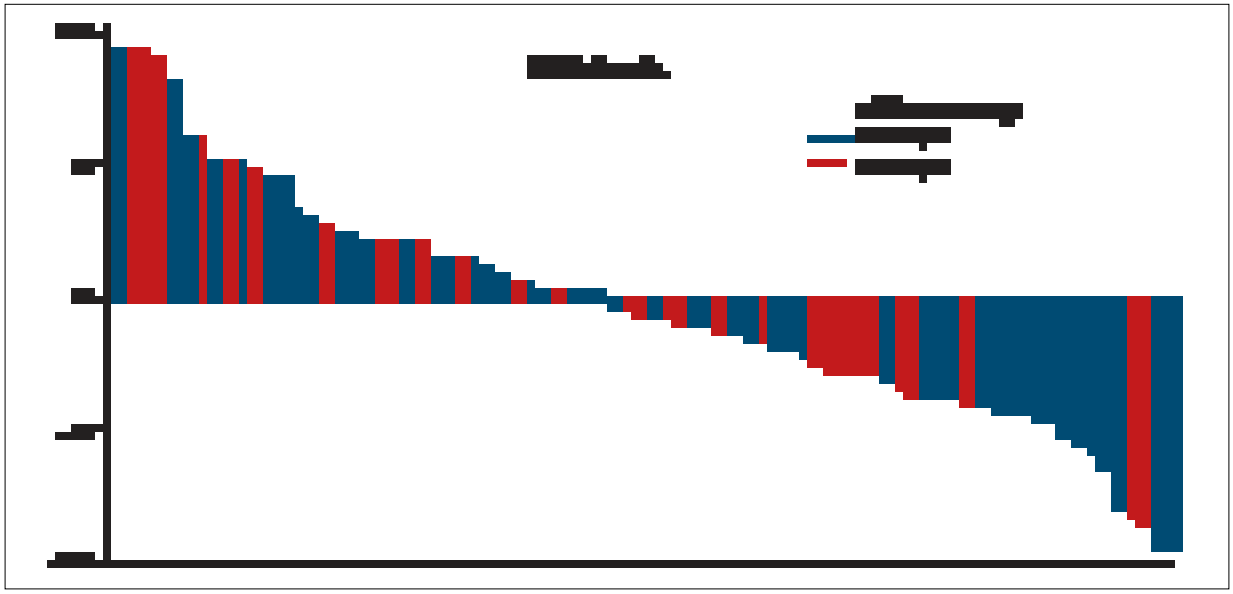


Figure 9. In a phase 2 trial, among the 49 patients who received PSMA ADC at 2.3 mg/kg, PSA levels declined by at least 30% in 36% of patients and declined by at least 50% in 15% of patients.

PSA, prostate-specific antigen; PSMA ADC, prostate-specific membrane antigen antibody-drug conjugate. Adapted from Petrylak DP et al. ASCO abstract 5023. *J Clin Oncol.* 2014;32(5 suppl).[37]

time to clinical progression (32.7 months vs 19.8 months; HR, 0.49; 95% CI, 0.37-0.65; *P*<.0001).

At the time of the analysis, 74% of patients with biochemical, symptomatic, or radiographic progression went on to receive docetaxel for CRPC. Subsequent therapies also included other chemotherapeutic agents, hormonal therapy, sipuleucel-T, and radiotherapy.

The safety analysis revealed a toxicity profile consistent with that previously reported for docetaxel. The most frequent grade 3/4 nonhematologic toxicity was fatigue, reported in 4% of patients. One patient died of sudden death. The most frequent grade 3/4 hematologic toxicities were neutropenia (12%) and febrile neutropenia (6%).

The investigators concluded that the addition of docetaxel is appropriate for patients starting ADT who are eligible for docetaxel. Dr Sweeney commented that for patients with a high volume of metastases, the demonstrated benefit of adding docetaxel justifies the burden of additional treatment. Conversely, for patients with a low volume of metastases, longer follow-up is required to better assess the role of adding docetaxel to ADT.

A Phase 2 Trial of Prostate Specific Membrane Antigen Antibody Drug Conjugate (PSMA ADC) in Taxane-Treated Metastatic Castration-Resistant Prostate Cancer

PSMA is a glycoprotein that is present at high levels on prostate cancer cells but has more limited expression in normal tissue outside the prostate. An antibody-drug conjugate (ADC) has been developed in which a monoclonal antibody directed against PSMA has been physically linked to the microtubule-disrupting agent monomethyl auristatin E (MMAE). At ASCO 2014, Dr Daniel P. Petrylak and colleagues presented the results of a phase 2 study evaluating the PSMA ADC in patients with taxane-treated mCRPC.[37] The study enrolled 83 patients with mCRPC who had progressed on abiraterone and/or enzalutamide and had also been treated with 1 to 2 prior chemotherapy regimens, including at least 1 taxane-containing regimen. The PSA ADC was administered every 3 weeks unless a dose delay was required. The first 34 patients received the PSMA ADC at a dose of 2.5 mg/kg. This dose was lowered to 2.3 mg/kg for all subsequent patients owing to neutropenia, which occurred at grade 3 or 4 severity in 32% of patients. Among the 49 patients who received PSMA ADC at 2.3 mg/kg, PSA levels declined by at least 30% in 36% of patients and declined by at least 50% in 15% of patients (Figure 9). Conversion from 5 CTC/mL or more at baseline to less than 5 after treatment was reported in 45% of patients. The investigators noted that expression of the target antigen, PSMA, was associated with PSA response and CTC response. Expression levels of neuroendocrine markers were also associated with responses. Among the 29 patients with low neuroendocrine marker expression, 76% of patients had CTC reductions of at least 50%. The 2.3 mg/kg dose was well tolerated; the most common grade 3 or higher adverse events were fatigue (18%), neutropenia (18%), and decreased electrolytes (10%). The PSMA ADC is currently being evaluated in a cohort of patients with mCRPC who have not previously received treatment with taxanes.[38]

Radium-223

Patient-Reported Quality of Life Analysis of Radium-223 Dichloride Evaluating Pain Relief From the Phase 3 ALSYMPCA Study

Radium-223 dichloride is an α emitter that selectively targets bone metastases. The randomized, double-blind ALSYMPCA (Alpharadin in Symptomatic Prostate Cancer Patients) trial compared radium-223 vs placebo in 921 patients with metastatic CRPC and bone metastases who had received docetaxel, were ineligible for docetaxel, or had declined docetaxel.[39] Patients were randomly assigned to receive 6 intravenous injections of radium-223 at 50 kBq/kg (406 patients) or matching placebo (168 patients), each administered once every 4 weeks in addition to the best standard of care. Radium-223 demonstrated a significant survival improvement, with a median OS of 14.9 months vs 11.3 months with placebo (HR, 0.70; 95% CI, 0.58-0.83; *P*<.001). Radium-223 was also associated with a delayed time to first external beam radiation therapy for bone pain (HR, 0.67; 95% CI, 0.53-0.85; *P*=.001) and, in a post hoc analysis, time to initial opioid use (HR, 0.62; 95% CI, 0.46-0.85; *P*=.002). At ASCO 2014, Dr Sten Nilsson and colleagues described patient-reported quality-of-life outcomes in the ALSYMPCA.[40] Improvements in pain were measured using the FACT-P questionnaire, completed at weeks 16 and 24, to obtain a pain-related score. These assessments were available for 70% of patients in the radium-223 arm and 63% of patients in the placebo arm at week 16, and for 57% and 48% of patients, respectively, at week 24. At each visit, a higher proportion of patients receiving radium-223 than placebo experienced a reduction in pain, defined as at least a 2-point decrease in the FACT-P pain-related score from baseline and no opioid use during treatment (Table 1). Although treatment with radium-223 was associated with higher rates of pain reduction than placebo, the majority of patients did not attain a pain response. Reduced pain was reported in 26% of radium-223–treated patients and 18% of placebo-treated patients at week 16 and in 25% and 13% of patients, respectively, at week 24. Overall, treatment with radium-223 was associated with a more than 2-fold increase in the likelihood of pain improvement at week 24 (odds ratio, 2.18; 95% CI, 1.17-4.06; *P*=.014). The effect of radium-223 on pain reduction was observed in all subgroups except patients with fewer than 6 bone metastases.

Table 1. Pain Improvement in the ALSYMPCA Trial

	Odds Ratio (Radium-223 vs Placebo)	95% CI	*P* Value
Week 16	1.70	1.08-2.70	.023
Week 24	2.18	1.17-4.06	.014
Weeks 16 and 24	2.58	1.18-5.62	.018

ALSYMPCA, Alpharadin in Symptomatic Prostate Cancer Patients. Data from Nilsson S et al. *J Clin Oncol.* 2014;32(5 suppl).[40]

1.5-Year Posttreatment Follow-Up of Radium-223 Dichloride Safety in Patients With Castration-Resistant Prostate Cancer and Symptomatic Bone Metastases From the Phase 3 ALSYMPCA Study

In the initial publication of the ALSYMPCA trial, radium-223 was associated with low rates of hematologic adverse events and fewer adverse events than placebo.[39] At ASCO 2014, Parker and colleagues presented posttreatment follow-up results from the phase 3 ALSYMPCA study, reporting on the long-term safety of radium-223.[41] The follow-up period started 4 weeks after the patients' last injection and ended 3 years after the first injection. A total of 574 patients, including 406 patients in the radium-223 arm and 168 patients in the placebo arm, entered the follow-up period. Overall, the long-term follow-up revealed no new safety concerns. Treatment-related adverse events were reported during the follow-up period in 6% of radium-223–treated patients and 5% of placebo-treated patients. The most common adverse events reported in the radium-223 arm were hematologic, including anemia (3%), neutropenia (1%, and thrombocytopenia (1%). No patients reported development of acute myeloid leukemia, myelodysplastic syndrome, or new primary bone cancer. One patient treated with radium-223 developed aplastic anemia that was considered probably related to the study medication. The investigators concluded that these long-term follow-up results support the continued evaluation of radium-223 in combination with other agents for the treatment of patients with mCRPC and symptomatic bone metastases.

A Biomarker Analysis

Androgen Receptor Splice Variant, AR-V7, and Resistance to Enzalutamide and Abiraterone in Men With Metastatic Castration-Resistant Prostate Cancer (mCRPC)

The role of AR splice variants in the development of resistance to AR-targeted therapy, covered briefly in the ASCO 2014 presentation of enzalutamide and abiraterone,[21] was discussed in more detail in a subsequent presentation by Dr Emmanuel S. Antonarakis.[25] Dr Antonarakis noted that mechanisms of response and resistance to AR-targeted agents in the setting of mCRPC are not well understood. Although AR splice variants could hypothetically contribute to the development of resistance against AR-targeted therapy, the clinical relevance of these variants has been unknown, particularly in the setting of novel AR-directed therapies.

In the phase 3 AFFIRM trial of enzalutamide, 21% of patients never attained a PSA decline and were therefore considered to have primary resistance.[17] Dr Antonarakis added that similar outcomes have been observed in clinical trials of abiraterone.[19] He noted that various potential mechanisms of resistance to AR-targeted agents have been proposed, including overexpression or upregulation of CYP17, activating mutations in the ligand-binding domain of AR, overexpression or amplification of AR, activation of relevant signaling pathways, upregulation of steroidogenic enzymes, glucocorticoid receptor–mediated transcriptional activation of androgen response elements, and AR splice variants (which have been proposed as a potential mechanism of resistance to both enzalutamide and abiraterone).

Dr Antonarakis explained that at least 20 AR splice variants (AR-Vs) have been identified. In the majority of cases, AR-Vs are composed of the first 3 exons of the AR gene followed by a cryptic exon that encodes for a premature stop codon, resulting in a truncated AR molecule. He said that the most important AR-V is AR-V7, for several reasons. First, AR-V7 is more abundant than other AR-Vs. Second, AR-V7 is constitutively active and is not sensitive to currently available AR-targeted therapies, as these therapies are directed against the ligand-binding domain of AR which is absent in AR-V7. Third, AR-V7 produces a translated protein product that is detectable in tissue and is not affected by nonsense-mediated mRNA decay. Finally, expression of AR-V7 is increased by approximately 20-fold in CRPC.

To investigate the role of AR-V7 in resistance to AR-targeted therapy, Antonarakis and colleagues conducted a prospective biomarker study evaluating the association between AR-V7 expression in CTC samples and responses to standard enzalutamide or abiraterone therapy in patients with CRPC. The prospective study included 30 men planning to start treatment with enzalutamide (31 patients) or abiraterone (31 patients). CTC samples were evaluated at baseline, at the time of response to AR-targeted therapy, and at the time of resistance to AR-targeted therapy. The investigators enriched the blood samples for CTCs, purified samples for prostate cancer mRNA, and measured mRNA expression of AR and AR-V7 using custom primers.

Of the 31 patients in the enzalutamide group, 60% of patients had a Gleason score of 8 or higher, and patients had received a mean of 3.3 prior hormonal therapies; 65% had received abiraterone and 65% had received docetaxel. Visceral metastases were present in 32% of patients, and the median PSA was 44.3 ng/mL.

Patients in the abiraterone group had a similar median age as those in the enzalutamide group (69 vs 70 years), and 73% of patients had a Gleason score of 8 or higher. Patients were less heavily pretreated than in the enzalutamide group; Dr Antonarakis commented that at his institution, abiraterone is typically used before enzalutamide. In the abiraterone group, patients had received a median of 2.5 prior hormonal therapies, 13% had received enzalutamide, and 16% had received docetaxel. Visceral metastases were present in 26% of patients. The baseline PSA was 37.8 ng/mL.

AR-V7 was detectable in 39% of patients in the enzalutamide group and 19% of patients in the abiraterone group. In both cohorts, AR-V7 was significantly associated with a lack of response to AR-directed therapy. The best PSA response rate in AR-V7–negative and AR-V7–positive patients was 53% and 0%, respectively (P=.004), in the enzalutamide group and 68% and 0%, respectively, in the abiraterone group (P=.004).

AR-V7–positive patients were significantly more likely than AR-V7–negative patients to develop PSA progression in both treatment groups, with a hazard ratio of 7.4 in the enzalutamide group (95% CI, 2.7-20.6; P<.001) and a hazard ratio of 16.1 in the abiraterone group (95% CI, 3.9-66.0; P<.001). Clinical and radiologic PFS outcomes were also significantly poorer in AR-V7–positive vs AR-V7–negative patients receiving either enzalutamide (HR, 8.5; 95% CI, 2.8-25.4; P<.001) or abiraterone (HR, 16.5; 95% CI, 3.3-82.9; P<.001).

In a pooled analysis of 58 patients treated with either enzalutamide or abiraterone, AR-V7 conversions from AR-V7–negative to AR-V7–positive occurred in 14% of patients. All patients with detectable AR-V7 at baseline remained AR-V7–positive.

Clinical outcomes in patients converting from AR-V7–negative to AR-V7–positive were intermediate. The PSA response rate in AR-V7–negative, AR-V7–converted, and AR-V7–positive patients was 68%, 17%, and 0%, respectively. The median PSA PFS was 6.1 months, 3.0 months, and 1.4 months, respectively, and the median PFS was 6.5 months, 3.2 months, and 2.1 months, respectively.

In the entire 62-patient cohort, AR-V7 was detected in 11.6% of patients prior to enzalutamide and abiraterone, 25.0% of patients with enzalutamide resistance, 51.2% of patients with abiraterone resistance, and 66.7% of patients with resistance to enzalutamide and abiraterone.

The investigators concluded that AR-V7 was expressed in a substantial proportion of patients with CRPC and could be detected in serial analyses of blood samples in patients receiving AR-targeting agents. AR-V7 was associated with responses to AR-targeting agents, suggesting a potential role in primary and secondary resistance to enzalutamide and abiraterone.

References

1. Hall SJ, GuhaThakurta D, Fan LQ, et al. Sipuleucel-T–induced antigen spread: immune response to prostate-specific antigen correlates with improved overall survival. Paper presented at: American Urological Association Annual Meeting; May 16-21, 2014; Orlando, Florida. Abstract 14-1585.
2. Sheikh NA, Petrylak D, Kantoff PW, et al. Sipuleucel-T immune parameters correlate with survival: an analysis of the randomized phase 3 clinical trials in men with castration-resistant prostate cancer. *Cancer Immunol Immunother*. 2013;62(1):137-147.
3. Kantoff PW, Higano CS, Shore ND, et al; IMPACT Study Investigators. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med*. 2010;363(5):411-422.
4. Morse MD, McNeel DG. Prostate cancer patients on androgen deprivation therapy develop persistent changes in adaptive immune responses. *Hum Immunol*. 2010;71(5):496-504.
5. Antonarakis ES, Kibel AS, Adams GW, et al. A randomized phase 2 study evaluating optimal sequencing of sipuleucel-T (sip-T) and androgen deprivation therapy (ADT) in biochemically recurrent prostate cancer [ASCO abstract 5041]. *J Clin Oncol*. 2014;32(5 suppl).
6. Pieczonka CM, Concepcion RS, Tutrone RF, et al. Time to chemotherapy following treatment with sipuleucel-T: data from PROCEED [ASCO abstract 5040]. *J Clin Oncol*. 2014;32(5 suppl).
7. ClinicalTrials.gov. A registry of sipuleucel-T therapy in men with advanced prostate cancer (PROCEED). http://clinicaltrials.gov/ct2/show/NCT01306890?term=01306890&rank=1. Identifier: NCT01306890. Accessed August 14, 2014.
8. Cooperberg M, Sartor O, Pieczonka C, et al. Treatment practice patterns in metastatic castration-resistant prostate cancer (mCRPC) patients prior to receiving sipuleucel-T: data from PROCEED. Paper presented at: American Urological Association Annual Meeting; May 16-21, 2014; Orlando, Florida. Abstract 14-444.
9. Aragon-Ching JB, Williams KM, Gulley JL. Impact of androgen-deprivation therapy on the immune system: implications for combination therapy of prostate cancer. *Front Biosci*. 2007;12(12):4957-4971.
10. Quinn DI, Petrylak DP, Pieczonka CM, et al. A randomized phase 2, open-label study of sipuleucel-T with concurrent or sequential enzalutamide in metastatic castration-resistant prostate cancer (mCRPC) [ASCO abstract e16071^]. *J Clin Oncol*. 2014;32(5 suppl).
11. ClinicalTrials.gov. Phase II study of sipuleucel-t and indoximod for patients with refractory metastatic prostate cancer. https://clinicaltrials.gov/ct2/show/NCT01560923?term=01560923&rank=1. Identifier: NCT01560923. Accessed August 14, 2014.
12. Jha GG, Miller JS, et al. A randomized, double-blind phase 2 study of sipuleucel-T followed by indoximod or placebo in the treatment of patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer [ASCO abstract TPS5111]. *J Clin Oncol*. 2014;32(5 suppl).
13. Pili R, Häggman M, Stadler WM, et al. Phase II randomized, double-blind, placebo-controlled study of tasquinimod in men with minimally symptomatic metastatic castrate-resistant prostate cancer. *J Clin Oncol*. 2011;29(30):4022-4028.
14. Shen L, Ciesielski M, Miles KM, et al. Modulation of suppressive myeloid populations by tasquinimod [AACR abstract nr 4746]. *Cancer Res*. 2013;73(8 suppl).
15. Pili R. A phase II randomized, open label study of sipuleucel−T versus sipuleucel−T and tasquinimod in patients with metastatic castrate-resistant prostate cancer (CRPC) [ASCO abstract TPS5110]. *J Clin Oncol*. 2014;32(5 suppl).
16. Tran C, Ouk S, Clegg NJ, et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. *Science*. 2009;324(5928):787-790.
17. Scher HI, Fizazi K, Saad F, et al; AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012;367(13):1187-1197.
18. Armstrong AJ, Tombal B, Sternberg CN, et al. Primary, secondary, and quality-of-life endpoint results from PREVAIL, a phase 3 study of enzalutamide in men with metastatic castration resistant prostate cancer (mCRPC) [ASCO abstract 5007]. *J Clin Oncol*. 2014;32(5 suppl).
19. Efstathiou E, Titus M, Tsavachidou D, et al. Effects of abiraterone acetate on androgen signaling in castrate-resistant prostate cancer in bone. *J Clin Oncol*. 2012;30(6):637-643.
20. Efstathiou E, Titus M, Wen S, et al. Molecular characterization of enzalutamide-treated bone metastatic castration-resistant prostate cancer [published online May 29, 2014]. *Eur Urol*. 2014 May 29. doi:10.1016/j.eururo.2014.05.005.
21. Efstathiou E, Titus M, Wen S, et al. Enzalutamide (ENZA) in combination with abiraterone acetate (AA) in bone metastatic castration resistant prostate cancer (mCRPC) [ASCO abstract 5000]. *J Clin Oncol*. 2014;32(5 suppl).
22. Scher HI, Fizazi K, Saad F, et al; AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012;367(13):1187-1197.
23. Li Y, Chan SC, Brand LJ, Hwang TH, Silverstein KA, Dehm SM. Androgen receptor splice variants mediate enzalutamide resistance in castration-resistant prostate cancer cell lines. *Cancer Res*. 2013;73(2):483-489.
24. Antonarakis ES, Lu C, Wang H, et al. Androgen receptor splice variant-7 predicts resistance to enzalutamide in patients with castration-resistant prostate cancer. Paper presented at: the 2014 Annual Meeting of the American Association for Cancer Research; April 5-9, 2014; San Diego, California. Abstract 2910.
25. Antonarakis ES, Lu C, Wang H, et al. Androgen receptor splice variant, AR-V7, and resistance to enzalutamide and abiraterone in men with metastatic castration-resistant prostate cancer (mCRPC) [ASCO abstract 5001]. *J Clin Oncol*. 2014;32(5 suppl).
26. Bolla M, Gonzalez D, Warde P, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. *N Engl J Med*. 1997;337(5):295-300.
27. McLeod DG, Iversen P, See WA, Morris T, Armstrong J, Wirth MP; Casodex Early Prostate Cancer Trialists' Group. Bicalutamide 150 mg plus standard care vs standard care alone for early prostate cancer. *BJU Int*. 2006;97(2):247-254.
28. Bolla M, de Reijke TM, Van Tienhoven G, et al; EORTC Radiation Oncology Group and Genito-Urinary Tract Cancer Group. Duration of androgen suppression in the treatment of prostate cancer. *N Engl J Med*. 2009;360(24):2516-2527.
29. Payne H, Mason M. Androgen deprivation therapy as adjuvant/neoadjuvant to radiotherapy for high-risk localised and locally advanced prostate cancer: recent developments. *Br J Cancer*. 2011;105(11):1628-1634.
30. Denham JW, Steigler A, Lamb DS, et al. Short-term neoadjuvant androgen deprivation and radiotherapy for locally advanced prostate cancer: 10-year data from the TROG 96.01 randomised trial. *Lancet Oncol*. 2011;12(5):451-459.
31. Denham JW, Joseph DJ, Lamb DS, et al. Main oncologic endpoints of the TROG 03.04 (RADAR) trial for men with locally advanced prostate cancer [ASCO abstract 5004]. *J Clin Oncol*. 2014;32(5 suppl).
32. Polascik TJ, Mouraviev V. Zoledronic acid in the management of metastatic bone disease. *Ther Clin Risk Manag*. 2008;4(1):261-268.
33. Dreicer R, MacLean D, Suri A, et al. Phase I/II trial of orteronel (TAK-700)—an investigational 17,20-lyase inhibitor—in patients with metastatic castration-resistant prostate cancer. *Clin Cancer Res*. 2014;20(5):1335-1344.
34. Dreicer R, Jones R, Oudard S, et al. 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) [ASCO GU abstract 7^]. *J Clin Oncol*. 2014;32:4(suppl).
35. De Wit R, Fizazi K, Jinga V, et al. Phase 3, randomized, placebo-controlled trial of orteronel (TAK-700) plus prednisone in patients (pts) with chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC) (ELM-PC 4 trial) [ASCO abstract 5008]. *J Clin Oncol*. 2014;32(5 suppl).

36. Sweeney C, Chen YH, Carducci MA, et al. Impact on overall survival (OS) with chemohormonal therapy versus hormonal therapy for hormone-sensitive newly metastatic prostate cancer (mPrCa): an ECOG-led phase III randomized trial [ASCO abstract LBA2]. *J Clin Oncol*. 2014;32(5 suppl).
37. Petrylak DP, Smith DC, Appleman LJ, et al. A phase 2 trial of prostate specific membrane antigen antibody drug conjugate (PSMA ADC) in taxane-treated metastatic castration-resistant prostate cancer [ASCO abstract 5023]. *J Clin Oncol*. 2014;32(5 suppl).
38. ClinicalTrials.gov. A study of PSMA ADC in subjects with metastatic castration-resistant prostate cancer (mCRPC). https://clinicaltrials.gov/ct2/show/NCT01695044?term=01695044&rank=1. Identifier: 01695044. Accessed August 14, 2014.
39. Parker C, Nilsson S, Heinrich D, et al; ALSYMPCA Investigators. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2013;369(3):213-223.
40. Nilsson S, Tomblyn M, Cislo P. Patient-reported quality of life analysis of radium-223 dichloride evaluating pain relief from the phase 3 ALSYMPCA study [ASCO abstract 5069]. *J Clin Oncol*. 2014;32(5 suppl).
41. Parker C, Vogelzang NJ, Sartor AO, et al. 1.5-year posttreatment follow-up of radium-223 dichloride safety in patients with castration-resistant prostate cancer and symptomatic bone metastases from the phase 3 ALSYMPCA study [ASCO abstract 5070]. *J Clin Oncol*. 2014;32(5 suppl).

Highlights in Advanced Prostate Cancer From the 2014 AUA and ASCO Meetings

Daniel J. George, MD
Associate Professor of Medicine and Surgery
Divisions of Medical Oncology and Urology
Duke University Medical Center
Durham, North Carolina

Presentations at the 2014 meetings of the American Urological Association (AUA) and the American Society of Clinical Oncology (ASCO) provided important new data on the management of advanced prostate cancer. Several studies focused on immunotherapy, next-generation androgen-deprivation therapy, chemotherapy, radium-223, and biomarkers.

Immunotherapy

At the AUA meeting, Dr Simon J. Hall presented results from a post-hoc analysis of the immune effects associated with sipuleucel-T treatment.[1] Sipuleucel-T is a targeted, specific immune therapy that stimulates prostate cancer recognition via the prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor fusion protein. There is increasing understanding, however, that this specific initial step has much broader results. In the study by Hall and colleagues, sipuleucel-T appeared to induce antigen spread; immunoglobulin G immune responses were detected against several secondary prostate tumor antigens.[1] This finding suggests that the immune activation associated with sipuleucel-T not only persists for months following the therapy, but it involves additional antigens in additional parts of the immune system. This finding provides important insight into the mechanisms of activity and resistance associated with sipuleucel-T by showing that this agent activates a broad array of antigens, which will be difficult for the cancer to overcome as the immune system begins to re-engage and recognize the cancer on multiple fronts. These exciting results are encouraging. It would be helpful to see similar studies in the prospective setting, but this analysis provides an important new step in understanding how a specific immunotherapy like sipuleucel-T could have even broader implications for immune activation.

At the ASCO meeting, Dr Emmanuel S. Antonarakis presented a phase 2 study evaluating the optimal sequencing of sipuleucel-T and antigen-deprivation therapy in biochemically recurrent prostate cancer.[2] The investigators reported similar sipuleucel-T–mediated immune activation regardless of which therapy was administered first. Patients who received sipuleucel-T first experienced greater antigen-specific T-cell responses. This study provides insight into the interplay between hormonal therapy and immunotherapy. Sipuleucel-T is not indicated for biochemically recurrent prostate cancer, and therefore this study is not likely to change the use of this agent. The study suggests, however, that the timing of immunotherapy and hormonal therapy is important. In the future, as studies evaluate immunotherapies in this disease setting and others—and, potentially, as secondary hormonal therapy—results like these can provide information on how best to sequence or combine these strategies to optimize the immune results and clinical benefit.

An analysis of data from PROCEED (PROVENGE Registry for Observation, Collection, and Evaluation of Experience Data), a large, prospective registry in the United States,[3] found that the time to subsequent therapy, specifically chemotherapy, after completion of sipuleucel-

T treatment was 1.5 months.[4] This finding is surprising for 2 reasons. First, it is substantially shorter than time to subsequent therapy in the IMPACT (Immunotherapy Prostate Adenocarcinoma Treatment) study, which was 14 weeks.[5] Second, patients receiving sipuleucel-T are largely asymptomatic or minimally symptomatic, and it is unlikely that most patients are becoming symptomatic in the month and a half after completion of sipuleucel-T. Therefore, this finding suggests that clinicians are not waiting for disease progression following sipuleucel-T therapy to initiate additional life-prolonging therapy, such as docetaxel-based chemotherapy. I find this approach encouraging because there is no reason to delay therapy in a patient with a limited life expectancy of 2 or 3 years. Chemotherapy can and should be used for its life-prolonging benefits rather than simply for its palliative benefits. It is interesting to note that the time to subsequent chemotherapy after sipuleucel-T was shorter for patients who were treated in medical oncology practices than in urology practices; it is possible that in urology practices, patients are receiving other secondary hormonal therapy rather than chemotherapy in the post–sipuleucel-T setting. A broader analysis of all subsequent therapies and prior therapies to sipuleucel-T is needed to fully elucidate practice patterns and understand how they may ultimately shape clinical benefits.

A study presented by Dr Matthew Cooperberg at the AUA meeting examined data from PROCEED to evaluate treatment practice patterns in oncology practices vs urology practices.[6] Patients treated at oncology practices were slightly younger, had slightly higher prostate-specific antigen levels, and were more likely to have received previous chemotherapy. It is not clear whether sipuleucel-T is driving a difference in referral patterns; many urology practices are equipped to administer sipuleucel-T and subsequently refer patients to medical oncology only when necessary. It is possible that sipuleucel-T practice patterns may change in the future, as there may be other therapies more commonly used in oncology practices vs urology practices or vice versa, which may widen the difference in the timing and use of sipuleucel-T in specialty practices.

A publication-only abstract from the ASCO meeting described results from a phase 2 study of sipuleucel-T with concurrent or sequential enzalutamide in metastatic castration-resistant disease.[7] The study results support the concomitant use of enzalutamide and sipuleucel-T in patients with metastatic castration-resistant prostate cancer (mCRPC). These results are important for 2 reasons. Data from the PREVAIL (A Safety and Efficacy Study of Oral MDV3100 in Chemotherapy-Naive Patients With Progressive Metastatic Prostate Cancer) trial showed that some patients with a good performance status are at risk of dying from prostate cancer in the 12 to 18 months after diagnosis and could still benefit from the addition of sipuleucel-T.[8] It is important to use sipuleucel-T concomitantly with enzalutamide rather than after patients develop resistance to enzalutamide and disease progression. Enzalutamide and sipuleucel-T employ noncompetitive mechanisms, the former targeting an androgen receptor–dependent biology and the latter having more broad mechanisms of activity that are not dependent on the androgen receptor. It should be possible to administer these agents concomitantly in clinical settings, and these new data strongly support that approach. The study demonstrates that there is no detriment to the presence of enzalutamide when the sipuleucel-T immunotherapy is created or administered.

Next-Generation Androgen-Deprivation Therapy

An analysis of the PREVAIL study[8] provided an in-depth evaluation of secondary and quality-of-life endpoints associated with the use of enzalutamide in patients with metastatic prostate cancer who were chemotherapy-naive.[9] This patient population includes a much broader population than patients previously treated with chemotherapy, in terms of number of patients, demographics, and characteristics. Many patients will not receive chemotherapy for various reasons, and it is important to evaluate their response to enzalutamide—specifically, the improvement in quality-of-life endpoints and secondary endpoints, including the delay in time to other interventions, such as chemotherapy; onset of pain; and other clinical manifestations associated with disease progression. The results of this analysis were consistent with the primary endpoint of overall survival. They suggest that there is an early separation in the survival of patients treated with enzalutamide vs placebo. Although placebo patients are likely to cross over early to other therapies, there is a survival advantage within the first 6 months that persists through to the median overall survival of 3 years. Importantly, this analysis showed that enzalutamide improved overall survival in men who are at risk of dying early from prostate cancer (within 12 to 18 months after diagnosis), a finding that differs from what was seen with other agents tested in this setting. The study suggests that early use of enzalutamide, specifically in patients who are at higher risk of early death from prostate cancer, is important.

Dr Eleni Efstathiou presented preliminary results from a single-institution study evaluating enzalutamide in combination with abiraterone in bone-metastatic, castration-resistant prostate cancer.[10] The results suggest that the combination of these agents could provide benefits but could also increase toxicities. Although these agents are both independently active in this disease setting, it is unclear

whether the combination is superior to the use of 1 agent alone. That question is being addressed in a large, phase 3 intergroup study led by the Alliance for Clinical Trials in Oncology and Dr Michael Morris, in which enzalutamide monotherapy is being compared with enzalutamide plus abiraterone.[11] This large, multicenter cooperative group study should be able to determine the efficacy and safety of the combination vs monotherapy. Findings from the study presented at ASCO support the rationale that is driving the phase 3 clinical trial.

Dr James William Denham presented results from a study of androgen suppression at 2 different durations, 18 months and 6 months, each with and without zoledronic acid.[12] The data were conflicting: 18 months of androgen suppression plus zoledronic acid was significantly more effective than 6 months of androgen suppression without zoledronic acid as assessed by the risk of prostate-specific antigen progression and the need for a secondary therapeutic intervention. In contrast, among the patients receiving 6 months of androgen suppression, use of zoledronic acid was associated with a shorter time to progression of prostate-specific antigen levels. It is important to note that these observations were based on secondary, subgroup analyses that were underpowered. My conclusion from this study is that the data show discrepant results, and further studies are needed to clarify the benefit and/or risk of zoledronic acid in this setting.

Dr Ronald De Wit presented results from a large, multinational, randomized phase 3 study evaluating an androgen synthesis inhibitor, orteronel, with prednisone vs prednisone alone in chemotherapy-naive mCRPC patients.[13] In previous studies in this setting, enzalutamide and abiraterone demonstrated significant clinical benefit.[9,14] Unfortunately, the study failed to meet its primary endpoint. The addition of orteronel did not significantly improve overall survival vs prednisone alone. In addition, a subgroup analysis did not identify any patient subsets that benefited from the addition of orteronel. Based on these less than robust results, this agent will not move forward in development. These findings underscore the risks of developing second-generation agents in a setting in which other agents have already demonstrated substantial efficacy. In the future, it will be important to identify agents that demonstrate activity independent of the use of other androgen-synthesis inhibitors or androgen-receptor antagonists in order to differentiate their clinical benefit and activity from those of established agents in the field.

Chemotherapy

The ASCO plenary session featured a fascinating late-breaking abstract presented by Dr Christopher J. Sweeney on the CHAARTED (Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer) study, a randomized trial for extensive disease in prostate cancer that compared chemohormonal therapy and androgen ablation.[15] This cooperative, intergroup study enrolled patients with de novo stage 4 metastatic prostate cancer. Patients were randomized to receive the standard of care—hormonal therapy (androgen ablation) alone—or hormonal therapy with the addition of 6 cycles of docetaxel chemotherapy (without prednisone). The study showed a remarkable 13.6-month improvement in median overall survival in favor of chemotherapy plus hormonal therapy vs hormonal therapy alone. In a previous study in the castration-resistant metastatic setting, docetaxel chemotherapy with prednisone increased survival by approximately 3 months as compared with mitoxantrone chemotherapy, but the use of mitoxantrone as the control arm likely narrowed the improvement in survival.[16] The 13.6-month improvement seen in the CHAARTED trial may reflect the importance of chemotherapy in the setting of the first androgen ablation for patients with metastatic prostate cancer, and suggests that there may be a critical window during which chemotherapy is much more beneficial. These results are exciting. Although further understanding of the mechanisms of interaction between hormonal therapy and chemotherapy is required, the CHAARTED results suggest that timing is important, and that combination therapies used in the right patient population can be dramatic in terms of their survival benefit. For a stage 4 disease setting, the 13.6-month improvement in overall survival with the addition of a single chemotherapy agent is unprecedented for solid tumors. These results, in my opinion, are the most important findings this year in oncology. Had this drug been a novel targeted agent, this study would likely have received far more recognition. It is important to not underestimate the benefits of this generic drug, and the use of chemotherapy plus hormonal therapy should be rapidly integrated into clinical practice for patients presenting with metastatic prostate cancer.

A phase 2 trial presented by Dr Daniel P. Petrylak evaluated a prostate-specific memory androgen antibody-drug conjugate (PSMA-ADC) in mCRPC patients who had received treatment with a taxane.[17] The novel therapy demonstrated clinical activity in a large proportion of patients in this setting. The results of this single-arm study were promising and provide rationale for a randomized trial to determine clinical efficacy. It should be noted that although the drug targeted PSMA, there was still some associated toxicity.

Radium-223

An analysis of pain relief in the ALSYMPCA (Alpharadin in Symptomatic Prostate Cancer Patients) study demonstrated that the overall survival benefit associated with radium-223 was not derived simply from a palliative

benefit.[18,19] The palliative benefit was relatively modest and not dramatically greater than what was seen in the placebo arm, in contrast to the difference in survival. This analysis supports the use of radium-223 in a broad array of patients with symptomatic prostate cancer, not just those patients who are dependent on narcotics for pain management. Therefore, radium-223 should be considered first for its overall survival benefit and second for any palliative quality-of-life benefits, in contrast to previous radiopharmaceuticals used in prostate cancer.

A follow-up analysis from the ALSYMPCA trial provided encouraging data.[20] During the relatively short, 1.5-year post-treatment follow-up period, there were no long-term toxicities associated with radium-223 administration. Importantly, there were no secondary malignancies or other delayed complications from systemic administration of radium-223. Longer-term follow-up data are eagerly awaited, but for now, these results strongly show that radium-223 has a favorable safety profile in patients with mCRPC.

A Biomarker Analysis

An informative analysis presented by Dr Emmanuel S. Antonarakis of patients treated at a single institution with secondary hormonal therapies demonstrated that the status of androgen receptor variant 7 (AR-V7) in circulating tumor cells had a significant impact on the clinical response to these therapies.[21] AR-V7 was detectable in 58% of patients, and it was significantly associated with a lack of response to androgen receptor–directed therapy. These results suggest that the presence of AR-V7 could be a marker of resistance, although further studies are needed to clarify the extent. The use of AR-V7, even as a marker, will require prospective evaluation, but this study provides the first indication of a marker or a biology that could be important in understanding which patients are likely to respond to hormonal therapies and which patients might require alternative strategies.

Acknowledgment

Dr George is a consultant for Algeta, Astellas, Aveo, Bayer, BMS, Dendreon, Exelixis, Medivation, Novartis, Pfizer, Progenics, Sanofi, Teva, and Viamet. He has received research support from Exelixis, Genentech/Roche, GSK, Janssen, Millennium/Takeda, Novartis, Pfizer, and Viamet. He is a speaker for Dendreon, Novartis, Pfizer, and Sanofi.

References

1. Hall SJ, GuhaThakurta D, Fan LQ, et al. Sipuleucel-T–induced antigen spread: immune response to prostate-specific antigen correlates with improved overall survival. Paper presented at: American Urological Association Annual Meeting; May 16-21, 2014; Orlando, Florida. Abstract 14-1585.

2. Antonarakis ES, Kibel AS, Adams GW, et al. A randomized phase 2 study evaluating optimal sequencing of sipuleucel-T (sip-T) and androgen deprivation therapy (ADT) in biochemically recurrent prostate cancer [ASCO abstract 5041]. *J Clin Oncol*. 2014;32(5 suppl).

3. ClinicalTrials.gov. A registry of sipuleucel-T therapy in men with advanced prostate cancer (PROCEED). http://clinicaltrials.gov/ct2/show/NCT01306890?term=01306890&rank=1. Identifier: NCT01306890. Accessed August 14, 2014.

4. Pieczonka CM, Concepcion RS, Tutrone RF, et al. Time to chemotherapy following treatment with sipuleucel-T: data from PROCEED [ASCO abstract 5040]. *J Clin Oncol*. 2014;32(5 suppl).

5. Kantoff PW, Higano CS, Shore ND, et al; IMPACT Study Investigators. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med*. 2010;363(5):411-422.

6. Cooperberg M, Sartor O, Pieczonka C, et al. Treatment practice patterns in metastatic castration-resistant prostate cancer (mCRPC) patients prior to receiving sipuleucel-T: data from PROCEED. Paper presented at: American Urological Association Annual Meeting; May 16-21, 2014; Orlando, Florida. Abstract 14-444.

7. Quinn DI, Petrylak DP, Pieczonka CM, et al. A randomized phase 2, open-label study of sipuleucel-T with concurrent or sequential enzalutamide in metastatic castration-resistant prostate cancer (mCRPC) [ASCO abstract e16071^]. *J Clin Oncol*. 2014;32(5 suppl).

8. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012;367:1187-1197.

9. Armstrong AJ, Tombal B, Sternberg CN, et al. Primary, secondary, and quality-of-life endpoint results from PREVAIL, a phase 3 study of enzalutamide in men with metastatic castration resistant prostate cancer (mCRPC) [ASCO abstract 5007]. *J Clin Oncol*. 2014;32(5 suppl).

10. Efstathiou E, Titus M, Wen S, et al. Enzalutamide (ENZA) in combination with abiraterone acetate (AA) in bone metastatic castration resistant prostate cancer (mCRPC) [ASCO abstract 5000]. *J Clin Oncol*. 2014;32(5 suppl).

11. ClinicalTrials.gov. Enzalutamide with or without abiraterone acetate and prednisone in treating patients with castration-resistant metastatic prostate cancer. https://clinicaltrials.gov/ct2/show/NCT01949337?term=enzalutamide+abiraterone&rank=5. Identifier: NCT01949337. Accessed August 15, 2014.

12. Denham JW, Joseph DJ, Lamb DS, et al. Main oncologic endpoints of the TROG 03.04 (RADAR) trial for men with locally advanced prostate cancer [ASCO abstract 5004]. *J Clin Oncol*. 2014;32(5 suppl).

13. De Wit R, Fizazi K, Jinga V, et al. Phase 3, randomized, placebo-controlled trial of orteronel (TAK-700) plus prednisone in patients (pts) with chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC) (ELM-PC 4 trial) [ASCO abstract 5008]. *J Clin Oncol*. 2014;32(5 suppl).

14. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med*. 2013;368(2):138-148.

15. Sweeney C, Chen YH, Carducci MA, et al. Impact on overall survival (OS) with chemohormonal therapy versus hormonal therapy for hormone-sensitive newly metastatic prostate cancer (mPrCa): an ECOG-led phase III randomized trial [ASCO abstract LBA2]. *J Clin Oncol*. 2014;32(5 suppl).

16. Tannock IF, de Wit R, Berry WR, et al; TAX 327 Investigators. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med*. 2004;351(15):1502-1512.

17. Petrylak DP, Smith DC, Appleman LJ, et al. A phase 2 trial of prostate specific membrane antigen antibody drug conjugate (PSMA ADC) in taxane-treated metastatic castration-resistant prostate cancer [ASCO abstract 5023]. *J Clin Oncol*. 2014;32(5 suppl).

18. Parker C, Nilsson S, Heinrich D, et al; ALSYMPCA Investigators. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2013;369(3):213-223.

19. Nilsson S, Tomblyn M, Cislo P. Patient-reported quality of life analysis of radium-223 dichloride evaluating pain relief from the phase 3 ALSYMPCA study [ASCO abstract 5069]. *J Clin Oncol*. 2014;32(5 suppl).

20. Parker C, Vogelzang NJ, Sartor AO, et al. 1.5-year posttreatment follow-up of radium-223 dichloride safety in patients with castration-resistant prostate cancer and symptomatic bone metastases from the phase 3 ALSYMPCA study [ASCO abstract 5070]. *J Clin Oncol*. 2014;32(5 suppl).

21. Antonarakis ES, Lu C, Wang H, et al. Androgen receptor splice variant, AR-V7, and resistance to enzalutamide and abiraterone in men with metastatic castration-resistant prostate cancer (mCRPC) [ASCO abstract 5001]. *J Clin Oncol*. 2014;32(5 suppl).

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

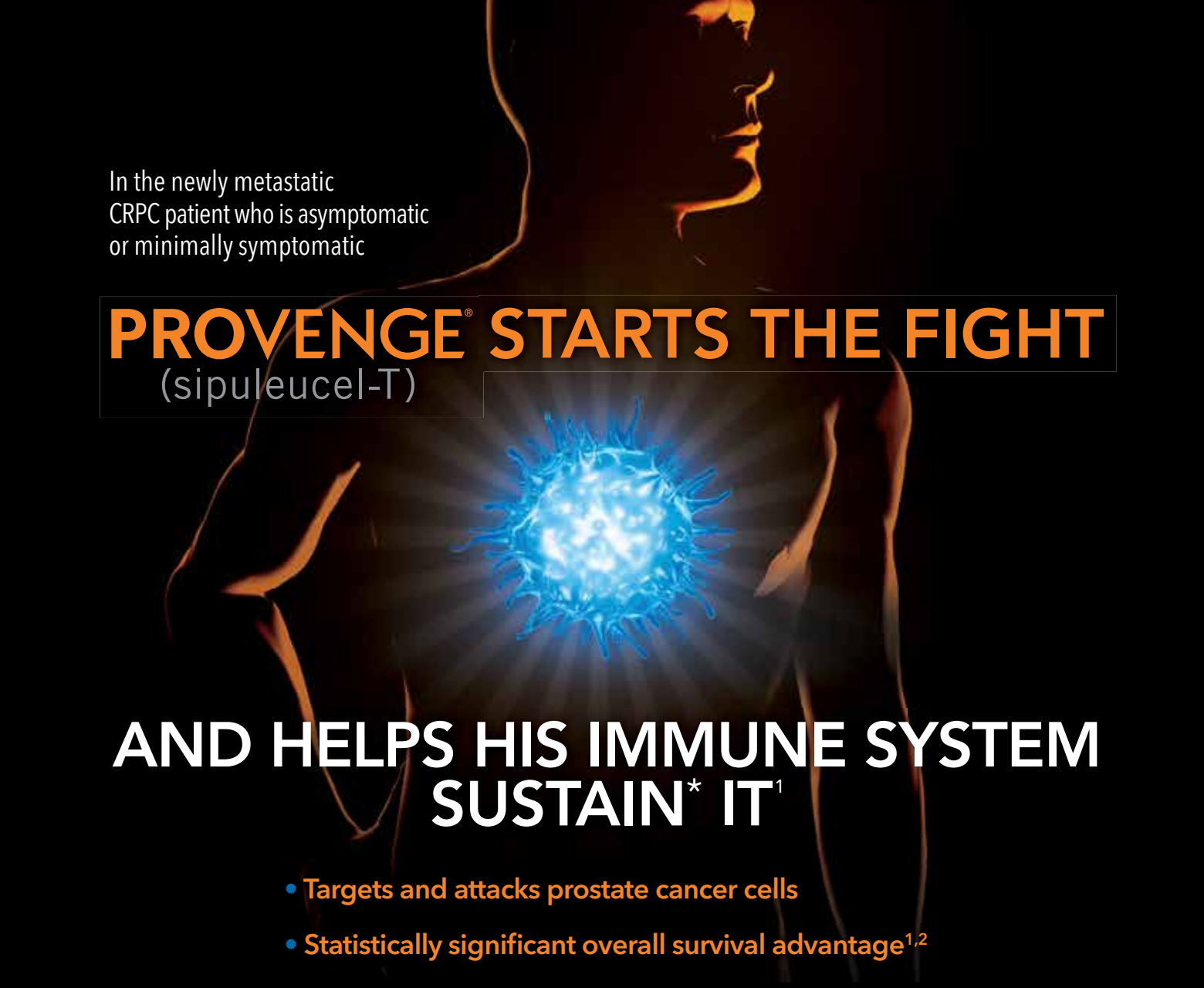
REFERENCES: 1. PROVENGE [package insert]. Dendreon Corporation; June 2011.
2. Kantoff PW, Higano CS, Shore ND, et al; for the IMPACT Study Investigators. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med*. 2010;363:411-422.

Dendreon®
on call
1-877-336-3736

Dendreon
Targeting Cancer, Transforming Lives®

www.PROVENGEReimbursement.com

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.

www.PROVENGEHCP.com