

# Clinical Roundtable Monograph

Clinical Advances in Hematology & Oncology

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## New and Emerging Treatments for Advanced Prostate Cancer

### PART 1 OF A 3-PART SERIES

#### Moderator



**Daniel J. George, MD**  
Director, Genitourinary Medical Oncology  
Director, Prostate Clinic  
Duke Medical Center  
Durham, North Carolina

#### Faculty



**Philip W. Kantoff, MD**  
Professor of Medicine  
Harvard Medical School  
Director, Lank Center for Genitourinary Oncology  
Dana-Farber Cancer Institute  
Boston, Massachusetts



**Daniel W. Lin, MD**  
Chief of Urologic Oncology  
Department of Urology  
University of Washington  
Seattle, Washington

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**Abstract:** Historically, the treatment of metastatic castration-resistant prostate cancer (CRPC) has been limited to chemotherapeutic regimens that did not improve patient survival. In 2004, clinical studies began to demonstrate significant improvements in patient outcomes, including overall survival, with docetaxel versus mitoxantrone chemotherapy. Since these pivotal trials, the combination of docetaxel plus prednisone has become a standard of care for patients with metastatic CRPC. However, the limited survival benefit achieved with this regimen prompted several investigations into the development of alternative therapeutic options. Recent advances have now led to an unprecedented number of new drug approvals within the past year, providing many new treatment options for patients with metastatic CRPC. Sipuleucel-T, considered a new paradigm in cancer treatment, is the first such immunotherapeutic agent approved by the US Food and Drug Administration. Other successes include abiraterone acetate, the first androgen biosynthesis inhibitor, and cabazitaxel, a novel microtubule inhibitor, both of which have demonstrated improved survival following docetaxel failure. The bone-targeting agent denosumab, also recently approved in this setting, offers these patients significant improvement in the prevention of skeletal-related events. The data supporting the approval of each of these agents are described in this monograph, as are current approaches in the treatment of metastatic CRPC and ongoing clinical trials of novel treatments and strategies. The experts also discuss several of the issues regarding the introduction of these novel agents into clinical practice for metastatic CRPC patients.

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**Target Audience:** This activity has been designed to meet the educational needs of oncologists and other healthcare professionals who treat patients with prostate cancer.

**Statement of Need/Program Overview:** Prostate cancer is the most common cancer in men. The traditional management approach had been with docetaxel, a chemotherapeutic agent associated with significant side effects. Patients with castration-resistant prostate cancer (CRPC) have evidence of prostate cancer progression in the setting of testosterone level suppression. In 2010, the US Food and Drug Administration approved 2 new agents for prostate cancer that will change the way the disease is managed. Sipuleucel-T was approved for asymptomatic or minimally symptomatic metastatic CRPC, providing a well-tolerated option for patients who may have received no treatment, were followed with close monitoring/watchful waiting, or received docetaxel. Cabazitaxel was approved for use in advanced metastatic CRPC in men who have previously been treated with docetaxel. Physicians must be aware of the data supporting these new agents, so that they can optimize their use with appropriate patient selection, timing of treatments, and sequencing of management approaches.

### Educational Objectives

After completing this activity, the participant should be better able to:

- Evaluate the roles of biomarkers and symptomatology in the assessment and treatment of patients with castration-resistant prostate cancer
- Describe recent clinical data on newly approved agents in the management of castration-resistant prostate cancer
- Identify patients who are most likely to benefit from newly approved agents
- Define strategies for integrating new agents into clinical practice

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# Benefits and Limitations of Current Treatment Strategies in Advanced Prostate Cancer

Daniel J. George, MD

The natural history of prostate cancer represents a long continuum of clinical states beginning with clinically localized disease, followed by biochemical failure and relapse in some patients, and then progression to metastatic disease. Ultimately, those patients who receive prolonged treatment with androgen-deprivation therapy (ADT) have an increased likelihood of developing castration-resistant prostate cancer (CRPC). This disease state is defined as having evidence of prostate cancer progression in the setting of testosterone level suppression (to <50 ng/mL), evidenced either as a rise in the prostate-specific antigen (PSA) level from nadir, or radiographic progression. (More rarely, clinical progression occurs in the absence of PSA progression.)

Although much focus has been on metastatic CRPC, the natural history of nonmetastatic CRPC is also important. In 2005, Smith and colleagues investigated a population of men with nonmetastatic CRPC in order to better define the natural history of this disease state.<sup>1</sup> In this study, 201 patients from the placebo arm of a discontinued randomized clinical trial were analyzed; all patients had prostate cancer with no radiographic evidence of metastases and PSA progression despite ADT. The median overall survival (OS) was not reached after a 2-year follow-up, and the median bone metastasis-free survival was 30 months. Two factors were found to independently predict a shorter time to first bone metastasis: baseline PSA level exceeding 10 ng/mL (relative risk [RR], 3.18; 95% confidence interval [CI], 1.74–5.80;  $P < .001$ ) and PSA velocity (RR, 4.34 for each 0.01 increase in PSA velocity; 95% CI, 2.30–8.21;  $P < .001$ ). Interestingly, these 2 factors were also found to be independently predictive of OS (RR for baseline PSA level >10 ng/mL: 3.19; 95% CI, 1.51–6.73;  $P = .002$ ; RR for PSA velocity, 1.39; 95% CI, 1.15–1.69;  $P < .001$ ) as well as metastasis-free survival (RR for baseline PSA level >10 ng/mL: 3.19; 95% CI, 1.84–5.53;  $P < .001$ ; RR for PSA velocity, 1.48; 95% CI, 1.25–1.74;  $P < .001$ ). Clinically, high PSA level and short doubling time may be useful parameters to identify patients with nonmetastatic CRPC who should be radiographically screened for development of new metastatic disease.

Until recently, the only treatment strategies available for patients with metastatic CRPC have been secondary

hormonal therapy (including the antiandrogens [nilutamide, flutamide, and bicalutamide] and androgen-suppressing agents [ketoconazole and estrogen]), traditional chemotherapeutics (docetaxel or mitoxantrone plus prednisone, and estramustine), and supportive care measures (such as bisphosphonates, erythropoietin, and palliative care agents). The main limitation of this armamentarium is that only 1 of these treatments—docetaxel plus prednisone—has been demonstrated to prolong patient survival in this setting. Although significant, this improvement in median OS was limited to only 2.9 months in the TAX 327 study compared with mitoxantrone plus prednisone (19.2 vs 16.3 months),<sup>2</sup> indicating there is still a lack of effect on the natural history of CRPC.

## Hormonal Therapy

Secondary hormonal therapy and androgen-suppressing agents have historically been used as inhibitors of steroidal hormone production. Although this has traditionally been thought to be primarily due to inhibition of steroid hormone production from the adrenal gland, recent evidence suggests that the prostate tumor itself may have steroid formation that can drive disease progression. Thus, these agents may actually have effects on hormone production within the tumor as well as within the adrenal gland. However, no prospective, randomized, phase III trials have yet demonstrated a survival advantage with these agents. Furthermore, their use is somewhat limited by tolerance, dosing, and ultimately, efficacy, in inhibiting steroid production. Therefore, their use in the setting of CRPC has largely been off-label, and primarily focused on modulating PSA progression without necessarily changing OS.

## Chemotherapy

In 1996, the combination of mitoxantrone plus prednisone was approved for the treatment of CRPC following a randomized study of 161 patients that showed the combination was superior to prednisone alone for the palliation of symptoms (29% vs 12%;  $P = .01$ ).<sup>3</sup> However, no difference in OS was observed between mitoxantrone

plus prednisone versus prednisone alone. Similarly, estramustine was also approved for treatment based on a palliative benefit.

It was not until 2004 that 2 independent, multicenter, phase III trials showed a survival advantage with chemotherapy. The international TAX 327 study randomized 1,006 men with metastatic CRPC to receive 1 of 2 docetaxel doses (75 mg/m<sup>2</sup> every 3 weeks or 30 mg/m<sup>2</sup> once weekly for 5 weeks) or 12 mg/m<sup>2</sup> mitoxantrone every 3 weeks; all patients also received 5 mg prednisone twice daily.<sup>4</sup> Patients receiving docetaxel every 3 weeks achieved a significant benefit in survival compared with patients in the mitoxantrone group (hazard ratio [HR] for death, 0.76; 95% CI, 0.62–0.94; *P*=.009). The median OS was 16.5, 18.9, and 17.4 months in the mitoxantrone, docetaxel-every-3-weeks, and weekly docetaxel arms, respectively. Patients in both docetaxel arms experienced a ≥50% decrease in the serum PSA level (*P*<.001 for both comparisons with mitoxantrone). Further, patients in both docetaxel arms achieved significant improvements in pain reduction and quality of life compared with mitoxantrone. In 2008, an updated survival analysis of the TAX 327 study was published, which showed that the significant survival benefit with docetaxel every 3 weeks compared with mitoxantrone persisted even with extended follow-up (*P*=.004).<sup>2</sup> The median OS was 16.3, 19.2, and 17.8 months in the mitoxantrone, docetaxel-every-3-weeks, and weekly docetaxel arms, respectively. It should be noted that the clinical significance of the approximately 3-month improvement in median OS achieved with docetaxel plus prednisone compared with mitoxantrone plus prednisone, as shown in the TAX 327 trial, has often been questioned—especially in light of the rigorous and long treatment schedule needed in order to achieve this benefit.

The second phase III trial that demonstrated a survival benefit with chemotherapy was the SWOG (Southwest Oncology Group) 916 study.<sup>5</sup> In this study, 770 men with metastatic CRPC were randomized to receive 21-day cycles of docetaxel (60 mg/m<sup>2</sup> on day 2), estramustine (280 mg 3 times daily on days 1–5), and dexamethasone (60 mg in 3 divided doses before docetaxel); or mitoxantrone (12 mg/m<sup>2</sup> on day 1) and prednisone (5 mg 2 times daily). Median OS was significantly prolonged in the docetaxel plus estramustine arm compared with the mitoxantrone plus prednisone arm (17.5 months vs 15.6 months; *P*=.02; HR for death, 0.80; 95% CI, 0.67–0.97). The median time to progression was approximately doubled in the docetaxel plus estramustine arm compared with the mitoxantrone plus prednisone arm (6.3 vs 3.2 months; *P*<.001). A 50% or higher decrease in the serum PSA level was experienced by a significantly greater proportion of patients in the

docetaxel plus estramustine arm compared with the mitoxantrone plus prednisone arm (50% vs 27%; *P*<.001).

## Bone-Targeting Therapies

The intravenous bisphosphonate zoledronic acid and the subcutaneous monoclonal antibody denosumab are both recommended by the National Comprehensive Cancer Network (NCCN) to prevent or delay skeletal-related events in patients with CRPC.<sup>6</sup>

The approval of zoledronic acid for this setting was largely dependent upon the results of a double-blind, phase III trial that randomized 643 men with CRPC and asymptomatic or minimally symptomatic bone metastases to receive either zoledronic acid (administered as 4 mg or 8 mg [subsequently reduced to 4 mg]) or placebo, both administered every 3 weeks for 15 months.<sup>7</sup> Skeletal-related events were prospectively defined as pathologic bone fractures (vertebral or nonvertebral), spinal cord compression, surgery to bone, radiation therapy to bone (including the use of radioisotopes), or a change of cancer therapy to treat bone pain. After a 15-month follow-up, more patients in the placebo arm experienced a skeletal-related event compared to those in the 4-mg zoledronic acid arm (33.2% vs 44.2%; *P*=.021). Further, patients in the 4-mg zoledronic acid arm demonstrated a prolonged median time to first skeletal-related event compared with patients in the placebo arm (not reached vs 321 days; *P*=.011). Patients who were treated with zoledronic acid also had significantly decreased urinary markers of bone resorption. The significant trend in improved outcomes with 4 mg zoledronic acid continued in an analysis of the long-term efficacy of zoledronic acid in 122 patients from this study.<sup>8</sup> In this long-term analysis, it was demonstrated that a skeletal-related event was experienced by fewer patients in the 4-mg zoledronic acid group compared with the placebo group (38% vs 49%; *P*=.028), with a significantly decreased annual incidence of skeletal-related events (0.77 vs 1.47; *P*=.005). Zoledronic acid also significantly delayed the median time to first skeletal-related event (488 days vs 321 days; *P*=.009). The ongoing risk of experiencing a skeletal-related event was reduced by 36% (risk ratio: 0.64, 95% CI, 0.485–0.845; *P*=.002) in the zoledronic acid arm versus the placebo arm.

The monoclonal antibody denosumab was recently demonstrated to be active in CRPC, and it may in fact be superior to zoledronic acid.<sup>9</sup> Denosumab will be discussed in more detail in the next section.

## Prognostic Factors

PSA levels may be a useful biomarker for identifying patients who are truly benefiting from therapy and in

whom treatment continuation is justified. A landmark analysis of the TAX 327 study showed that PSA response was a significant predictor of OS (6-month HR, 0.46; 95% CI, 0.40–0.54;  $P < .001$ ).<sup>10</sup> In fact, patients who achieved a PSA response lived significantly longer than patients who did not achieve a PSA response (HR, 0.45; 95% CI, 0.39–0.53;  $P < .001$ ). Compared with patients who did not achieve a 30% or greater decline in PSA levels, those who did demonstrated a significantly lower rate of visceral metastases (20% vs 28%;  $P = .03$ ).<sup>11</sup>

The Prostate Cancer Clinical Trials Working Group has defined clinical subtypes of metastatic CRPC based on pattern of disease spread.<sup>12</sup> These subtypes include 1) locally progressing tumors with no evidence of metastasis; 2) rising PSA levels with no evidence of metastasis; 3) nodal spread with no detectable bone or visceral (lung or liver) metastasis; 4) bone disease with or without nodal spread and no detectable visceral metastasis; and 5) visceral metastasis with or without spread at other sites. These subtypes have widely varied natural histories, suggesting they may respond differently to treatment. Indeed, a recent analysis of data from the TAX 327 study showed that in the 3 subtypes identified among randomized patients (node-only, bone spread with or without node disease, and visceral disease), the proportion of patients who achieved a 30% or greater decline in PSA was 79%, 61%, and 51%, respectively ( $P < .0001$ ).<sup>11</sup> The corresponding rates of median OS were 35.0, 19.5, and 14.5 months, respectively ( $P < .0001$ ). Thus, the pattern of metastasis may also be helpful in understanding which patients would most benefit from chemotherapy.

## Conclusion

Based on the pivotal TAX 327 and the SWOG 916 studies, docetaxel plus prednisone remains the standard of care for the treatment of metastatic CRPC.<sup>6</sup> However, the survival benefit demonstrated in these studies is minimal. In order to prolong OS for patients with CRPC and truly change the natural history of the disease, novel therapies are needed both before and after docetaxel treatment.

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# Newly Approved Agents for Castration-Resistant Prostate Cancer

Philip W. Kantoff, MD

The past year has seen unprecedented advances in prostate cancer research, and several new agents have gained US Food and Drug Administration (FDA) approval for the treatment of prostate cancer. The following is a short summary of some of the recent major advances in this field.

## Sipuleucel-T

The individualized dendritic cell vaccine sipuleucel-T represents the first FDA-approved agent in a novel immunotherapeutic class of agents. The treatment begins with leukapheresis to isolate peripheral blood mononuclear cells. Antigen-presenting cells, including dendritic cells, are then activated by exposing the peripheral blood mononuclear cells to a PAP-GM-CSF recombinant protein fusion comprised of the prostatic acid phosphatase (PAP) fused with human granulocyte-macrophage colony-stimulating factor (GM-CSF). These treated cells are then reinfused into the patient. The entire process (leukapheresis and in vitro PAP-GM-CSF treatment followed by reinfusion) is repeated every 2 weeks for a total of 3 treatments.

Initial results from phase III trials with sipuleucel-T failed to meet their primary endpoint of progression-free survival (PFS), but showed evidence of a benefit in OS. For example, in a study of 127 patients with CRPC who were randomized to either sipuleucel-T or placebo, the median time to progression was 11.7 weeks and 10.0 weeks, respectively (HR, 1.45, 95% CI, 0.99–2.11;  $P=.52$ ).<sup>1</sup> However, the median OS was 25.9 versus 21.4 months for the sipuleucel-T and placebo arms, respectively (HR, 1.70; 95% CI, 1.13–2.56;  $P=.01$ ). An integrated analysis of 225 patients randomized in 2 phase III studies demonstrated a 33% reduction in the risk of death for patients who received sipuleucel-T compared with placebo (HR, 1.50; 95% CI, 1.10–2.05;  $P=.011$ ).<sup>2</sup>

Based on these promising OS data, IMPACT (Immunotherapy Prostate Adenocarcinoma Treatment), a large, double-blind, placebo-controlled, multicenter, phase III trial, was initiated.<sup>3</sup> Unlike the prior studies, the primary endpoint of the IMPACT study was OS. A total of 512 patients with either asymptomatic or minimally

symptomatic metastatic CRPC were randomized in a 2:1 ratio to receive either sipuleucel-T or placebo. Compared with the placebo arm, patients in the sipuleucel-T arm achieved a 22% relative reduction in the risk of death (HR, 0.78; 95% CI, 0.61–0.98;  $P=.03$ ). This reduction represented a 4.1-month increase in median OS between the placebo and sipuleucel-T arms (21.7 months vs 25.8 months). The rate of 3-year OS was also increased with sipuleucel-T compared with placebo (31.7% vs 23.0%). Despite the improvements in survival, there was no significant difference achieved in the PSA response or time to progression between the 2 treatment arms. Importantly, sipuleucel-T treatment was well tolerated; the adverse events reported, including fevers, chills, fatigue, nausea, and headache, were consistent with a cytokine-mediated infusion reaction, were transient, and were mostly low grade.

Sipuleucel-T received FDA approval in April 2010 for the treatment of patients with asymptomatic or minimally symptomatic metastatic CRPC.<sup>4</sup> Several questions regarding sipuleucel-T remain unanswered. For example, the optimal timing of treatment is not clear: should it be administered as soon as possible in patients or following secondary hormonal therapy or chemotherapy? There is a concern it may be detrimental to administer concomitant corticosteroids and sipuleucel-T, and the IMPACT trial required a 4-week washout period. The use of sipuleucel-T in combination with other therapeutic agents besides ADT remains to be investigated.

## Abiraterone Acetate

The standard initial therapy for advanced prostate cancer is ADT. Many of these patients ultimately develop CRPC, evidenced as disease progression in the setting of castrate serum levels of testosterone. However, it is now well recognized that the androgen receptor remains an important signaling pathway in the setting of CRPC. Several mechanisms of androgen resistance have been suggested. For example, “hypersensitization” of the androgen receptor, either through gene amplification or activating mutations, may make the receptor more susceptible to stimulation by circulating androgens. Further, increased

local intracrine androgen synthesis may allow for a higher level of androgen receptor stimulation. Despite the overwhelming evidence suggesting the importance that androgen receptor signaling continues to have in CRPC, androgen signaling blocking agents had not been demonstrated to prolong patient survival until recently.

In April 2011, abiraterone acetate was approved by the FDA for the treatment of metastatic CRPC following progression on docetaxel therapy.<sup>5</sup> Abiraterone acetate is the first agent in this drug class that has been demonstrated to have an impact on the natural history of prostate cancer disease. In the pivotal multicenter COU-AA-301 trial, 1,195 patients with metastatic CRPC were randomized to receive treatment with either abiraterone (1,000 mg) or placebo, both given with prednisone (5 mg twice daily).<sup>6</sup> Treatment was continued until disease progression or unacceptable toxicity; patients with prior ketoconazole treatment for prostate cancer were excluded from this study. In an interim analysis, several outcomes were found to be significantly improved in the abiraterone group compared with the placebo group, including the median OS (14.8 vs 10.9 months, HR, 0.646; 95% CI, 0.543–0.768;  $P < .0001$ ), the time to PSA progression (10.2 vs 6.6 months;  $P < .0001$ ), and radiographic PFS (5.6 vs 3.6 months;  $P < .0001$ ). In addition, a greater proportion of patients in the abiraterone arm achieved a PSA response (38% vs 10%;  $P < .0001$ ). For the subset of patients who had received only 1 prior chemotherapy, the median OS was 15.8 months for patients who received abiraterone acetate compared with 11.2 months for patients who received the placebo (HR, 0.740; 95% CI, 0.638–0.859).<sup>5</sup>

COU-AA-302 is a similar ongoing study that is evaluating the efficacy of abiraterone in metastatic CRPC patients who have not yet been treated with docetaxel. The results of this trial are expected soon.

## Denosumab

Denosumab is a monoclonal antibody directed against the receptor activator of the nuclear factor  $\kappa$  B ligand (RANKL). As such, denosumab inhibits the bone resorption function of osteoclasts and thus delays bone destruction.

Denosumab was evaluated in a phase III trial of ADT-related bone loss.<sup>7</sup> In this study, 1,468 patients were randomized to receive either denosumab (60 mg) or placebo every 6 months. After 2 years, the lumbar spine bone mineral density increased by 5.6% in the denosumab arm, whereas it decreased by 1.0% in the placebo arm ( $P < .001$ ). Similar increases in the bone mineral density of the total hip, femoral hip, and distal third of the radius were also reported in the denosumab group. These

improvements led to a significantly decreased 3-year incidence of new vertebral fractures among patients in the denosumab-treated group ( $P = .006$ ).

In order to determine if denosumab could prevent skeletal-related events in CRPC patients with bone metastases, it was compared to zoledronic acid in a randomized, double-blind, placebo-controlled phase III trial that included 1,904 CRPC patients with no prior exposure to intravenous bisphosphonate.<sup>8</sup> Patients were randomized to receive either 120 mg denosumab or 4 mg zoledronic acid, both given with placebo (intravenous or subcutaneous for denosumab or zoledronic acid, respectively) every 4 weeks. The median time to first skeletal-related event was prolonged in the denosumab arm compared with the zoledronic acid arm (20.7 vs 17.1 months, HR, 0.82, 95% CI, 0.71–0.95;  $P = .0002$  for non-inferiority and  $P = .008$  for superiority). The rate of adverse events was relatively similar between the 2 treatment arms, including similar rates of osteonecrosis of the jaw.

In November 2010, the FDA approved denosumab for the prevention of skeletal-related events in patients with bone metastases from solid tumors.<sup>9</sup> Based on its efficacy in patients with prostate cancer, denosumab is a reasonable alternative to zoledronic acid in metastatic CRPC patients.

## Cabazitaxel

Until recently, there were no chemotherapeutic options approved for the treatment of CRPC following progression on docetaxel. However, this was changed with the FDA approval of the novel tubulin-binding microtubule inhibiting agent cabazitaxel. The approval of cabazitaxel in this setting was largely based on the positive results of the TROPIC (Treatment of Hormone-Refractory Metastatic Prostate Cancer Previously Treated With a Taxotere-Containing Regimen) trial.

TROPIC was an open-label, randomized, phase III trial in 755 men with metastatic CRPC.<sup>10</sup> All patients had received prior hormonal therapy. Patients were treated every 3 weeks with either cabazitaxel (25 mg/m<sup>2</sup>) or mitoxantrone (12 mg/m<sup>2</sup>), both administered with prednisone (10 mg/day). Patients were treated either until disease progression, unacceptable toxicity, or completion of 10 therapy cycles. The median OS was significantly prolonged in the cabazitaxel plus prednisone arm compared with the mitoxantrone plus prednisone arm (15.1 vs 12.7 months, HR, 0.70; 95% CI, 0.59–0.83;  $P < .0001$ ). Significantly, patients in the cabazitaxel arm also achieved a significant increase in PFS (2.8 vs 1.4 months, HR, 0.74; 95% CI, 0.64–0.86;  $P < .0001$ ). Response rates according to investigator assessment were also higher for cabazitaxel-treated

patients compared with mitoxantrone-treated patients (14.4% vs 4.4%;  $P=.0005$ ); no complete responses were observed in either group. Grade 3 or higher neutropenia (82% vs 58%) and febrile neutropenia (8% vs 1%) were higher in the cabazitaxel arm compared with the mitoxantrone arm. Because of this, patients may benefit from concomitant administration of granulocyte colony-stimulating factor (G-CSF). Based on these results, in June 2010, the FDA approved cabazitaxel for the second-line treatment of patients with advanced hormone-refractory prostate cancer following docetaxel treatment.<sup>11</sup>

## Conclusion

Data for 4 newly approved agents for patients with CRPC were summarized here. Significant among these agents are those that have demonstrated an improvement in OS, as very few agents have been shown to achieve this endpoint in the setting of metastatic CRPC.

## Acknowledgment

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# Promising Agents Under Clinical Investigation in Castration-Resistant Prostate Cancer

Daniel W. Lin, MD

With the recent introduction of several FDA-approved agents to treat prostate cancer, it is certainly a landmark time in this changing field. In addition, an array of novel agents are currently in phase II and phase III clinical trials; many of them hold great promise for improving the morbidity and mortality of prostate cancer patients. Much of this emerging research is occurring for the treatment of later-stage metastatic CRPC.

## Targeting the Androgen Receptor Pathway

As has already been discussed, the androgen receptor has been found to remain a viable target, even in the setting

of CRPC. The success of this strategy was recently shown with the approval of abiraterone acetate following the success of the COU-AA-301 trial, which demonstrated a significant survival benefit compared with placebo (median OS, 14.8 vs 10.9 months; HR, 0.646; 95% CI, 0.543–0.768;  $P<.0001$ ).<sup>1</sup>

Although the primary mechanism of action of abiraterone is to block the production of androgens, several other agents have been developed with the goal of inhibiting the interaction between androgens and the androgen receptor. One of these novel agents is MDV3100, an extremely potent androgen receptor inhibitor that binds to the receptor with a very high affinity (even greater than traditional inhibitors such as bicalutamide).<sup>2</sup> In



addition, MDV3100 also inhibits the subsequent translocation of the androgen receptor complex to the nucleus, thereby preventing downstream activation of the androgen receptor-responsive pathways. Importantly, MDV3100 is an orally available compound, making it easier to administer than intravenous agents. MDV3100 has shown great promise in phase II clinical trials. In one particular trial of 140 patients with metastatic CRPC, MDV3100 treatment resulted in impressive declines in PSA levels ( $\geq 50\%$  in 56% of patients).<sup>3</sup> This study population included both chemotherapy-naïve patients and patients who had failed prior docetaxel therapy.

MDV3100 is currently under evaluation in 2 large, global, phase III clinical trials. In the AFFIRM (A Study Evaluating the Efficacy and Safety of Investigational Drug MDV3100 in Men with Advanced Prostate Cancer) study, metastatic CRPC patients who have previously failed docetaxel treatment are being randomized in a blinded fashion to treatment with either MDV3100 or placebo (2:1), with a primary study endpoint of OS.<sup>4</sup> The study is fully accrued, but results have not yet been reported. The second study, PREVAIL (A Safety and Efficacy Study of Oral MDV3100 in Chemotherapy-Naïve Patients With Progressive Metastatic Prostate Cancer), is investigating the efficacy of MDV3100 in the prechemotherapy setting.<sup>5</sup> This trial will enroll 1,680 patients with chemotherapy-naïve metastatic CRPC who have failed ADT. Patients will be randomized to treatment with either MDV3100 or placebo (1:1), with OS and PFS as the primary endpoints. Accrual to this study is ongoing.

Another emerging agent in this drug class, TAK-700, is under investigation in phase III clinical trials. TAK-700 is an orally available, selective nonsteroidal androgen synthesis inhibitor. TAK-700 exerts its action by specifically targeting CYP17, a key enzyme involved in the production of DHEA, a precursor for androgen synthesis in the testes and adrenal glands.<sup>6</sup> Thus, this agent will likely be able to inhibit the persistent extragonadal synthesis of androgens. Several phase II and phase III clinical trials evaluating TAK-700 in different settings of metastatic CRPC are currently recruiting.<sup>7-10</sup>

### Targeted Agents

A number of novel targeted agents that inhibit specific pathways or proteins important for prostate cancer cell survival are under investigation for metastatic CRPC. OGX-11 is an inhibitor of the clusterin protein, a cytoprotective chaperone protein that acts similarly to heat shock proteins.<sup>11</sup> The transcription of clusterin is promoted by the androgen receptor, and the high expression of clusterin in prostate cancer has been found to correlate with Gleason grade.<sup>12</sup> Interestingly, the expression of clusterin

increases following ADT, and it is notably very high in patients with CRPC.<sup>13</sup> In several studies, overexpression of clusterin has been shown to confer a survival advantage with resistance to several agents, including hormonal therapy, chemotherapy, and radiation therapy.<sup>13,14</sup>

OGX-11 is an antisense oligonucleotide with a sequence that is complementary to the clusterin mRNA.<sup>15</sup> Administration of OGX-11 is expected to inhibit clusterin translation and thus lead to reduced clusterin expression. In a phase II study of 81 patients with chemotherapy-naïve metastatic CRPC, patients were randomized to treatment with docetaxel plus prednisone administered either with or without the addition of OGX-11.<sup>16</sup> Patients who received the added OGX-11 achieved a significant improvement in OS, even after adjusting for several factors in a multivariate analysis (HR, 0.49;  $P=.012$ ).

A similarly designed phase III clinical trial evaluating the addition of OGX-11 to standard chemotherapy is currently under way.<sup>17</sup> This study is planned to recruit 800 patients with chemotherapy-naïve metastatic CRPC. The primary study endpoint, OS, will be assessed after patients are randomized to treatment with docetaxel plus prednisone either alone or with OGX-11.

Although the novel agent XL-184 is still early in clinical development, it has demonstrated exciting results in a preliminary phase II clinical trial. XL-184 is a potent inhibitor of both MET and the vascular endothelial growth factor receptor 2 pathways involved in proliferation and angiogenesis.<sup>18</sup> In a limited phase II clinical trial that included 72 patients with both chemotherapy-naïve and chemotherapy-resistant metastatic CRPC, treatment with XL-184 was associated with dramatic (nearly complete) resolution of bone metastases on bone scan in 87% of patients following 12 weeks of therapy as well as impressive pain response in many of these cases.<sup>19</sup> Phase III trials with this agent are currently being planned.

Another promising treatment is radium-223 chloride, which is undergoing evaluation in the phase III ALSYMPCA (Alpharadin in Symptomatic Prostate Cancer) trial in patients with CRPC and symptomatic bone metastases. The agent met its primary endpoint by significantly improving OS, which was 14.0 months in the radium-223 chloride arm and 11.2 months in the placebo arm (HR, 0.699; 2-sided  $P=.0022$ ). Based on a recommendation from the Independent Data Monitoring Committee, the study will be stopped, and patients in the placebo arm will be offered treatment with radium-223 chloride.<sup>20</sup>

### Novel Immunotherapeutics

Based on the exciting recent success of the immunotherapy agent sipuleucel-T, several other immunotherapeutic approaches are under investigation in metastatic CRPC.

Examples include passive immunotherapy (the transfer of monoclonal antibodies or other immunologic agents), active immunotherapy (vaccines), and gene therapy.

One exciting approach involves modulation of the T-cell regulation and activation, a process termed T<sub>Reg</sub> manipulation. The compound being investigated for this approach is ipilimumab (MDX010), a monoclonal antibody that targets the immune checkpoint molecule cytotoxic T-lymphocyte antigen 4 (CTLA-4). Ipilimumab acts by blocking T-cell activation, with subsequent enhancement of T-cell responses and thus cell death. Early clinical trials showed promising results with this agent,<sup>21</sup> leading to the initiation of 2 phase III clinical trials. One of these studies is planned for approximately 600 metastatic CRPC patients with chemotherapy-naïve disease,<sup>22</sup> and the other is planned for approximately 800 metastatic CRPC patients who have failed prior docetaxel treatment.<sup>23</sup> Notably, ipilimumab recently received approval from the FDA for the treatment of melanoma.<sup>24</sup>

A second promising immunotherapy in prostate cancer is PROSTVAC, a vaccinia vector-based immunotherapy that utilizes pox virus vectors that express PSA and 3 T-cell costimulatory molecules: intercellular adhesion molecule 1 (ICAM-1 or CD54), B7-1 (CD80), and leukocyte function-associated antigen 3 (CD58). Data from a recently published, randomized phase II trial showed promising benefits in OS among patients with chemotherapy-naïve metastatic CRPC.<sup>25</sup> The 3-year post-study OS was 30% versus 17% among patients treated with PROSTVAC versus placebo, respectively. The median OS was 25.1 versus 16.6 months, respectively (HR, 0.56; 95% CI, 0.37–0.85;  $P=0.0061$ ).

## Conclusion

There is a wide array of additional agents that are either already in phase III trials or are close to evaluation in advanced clinical studies. Novel targeted therapies, including angiogenesis inhibitors, lenalidomide, and radiopharmaceuticals, are being tested in combination with cytotoxic chemotherapeutic agents, such as docetaxel. It is an exciting time for the field of prostate cancer therapy, with many advances and newly available therapeutics. It is worthy to note that although many new agents target novel mechanisms, many others target well-established mechanisms. Regardless, these agents are leading to important advances in improving the survival of patients with metastatic CRPC.

## Acknowledgment

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## Discussion

**Philip W. Kantoff, MD** A decline of 30% or more in PSA levels is commonly reported as a clinical measurement of benefit following docetaxel treatment in patients with CRPC.<sup>1</sup> In my clinical practice, there are many patients who instead exhibit a stabilization of PSA level. Is this an adequate measurement of response to chemotherapy, or should these patients be switched to a different treatment?

**Daniel J. George, MD** I agree with the use of PSA stabilization as a surrogate marker of docetaxel response. The use of a PSA decline of 30% or more is common but limited in the identification of a number of patients who are benefiting from docetaxel treatment but do not necessarily achieve a robust decrease in PSA level. When a patient achieves the 30% or greater PSA decline, I am more confident in progressing with docetaxel chemotherapy and will thus modify it as needed in the case of significant toxicity. For patients who instead show stabilization of the PSA level but no other signs of disease progression, I am still comfortable continuing treatment, provided the patient is tolerating docetaxel therapy. However, if there are signs of significant toxicity, I am more hesitant to continue treatment if the patient is not exhibiting any other signs of response.

**Daniel W. Lin, MD** Many urologists, especially those in the community setting, are often faced with patients who have nonmetastatic CRPC. What strategy do you recommend for more rigorous screening of patients with nonmetastatic CRPC, in order to better identify those who are progressing on hormonal therapy without any visible radiographic metastasis?

**Daniel J. George, MD** This is a very important point. I do not think there has been publication of any strong recommendations on screening in this population. However, I think there is an absolute need for a better modality to image this disease more directly. Based on the 2005 study by Smith and colleagues,<sup>2</sup> it seems that for a relatively low-risk patient population, screening every 6–12 months is likely reasonable. Conversely, for patients at higher risk of developing bone metastatic disease within 1 year (patients with PSA doubling time <6 months or PSA value >20 ng/mL), it is probably more reasonable to perform imaging every 3–4 months. This approach recognizes that the natural history of these patients, once they develop bone metastatic disease, is associated with a 2–4 year median survival. Thus, the need to identify and treat these patients early in order to prolong survival overcomes the cumulative risk of radiation exposure.

**Daniel W. Lin, MD** This likely also will help to make them eligible for novel therapies earlier in their disease course.

**Daniel J. George, MD** Yes, exactly. We definitely do not want to miss an opportunity to treat these patients while they are in an early asymptomatic state. To do so would ultimately limit our treatment options to chemotherapy alone.

**Daniel W. Lin, MD** Can you please comment on some of the newer imaging techniques for this setting?

**Daniel J. George, MD** Unfortunately, we do not have very accurate imaging of the cancer epithelial tumor cell component itself. Instead, we are really measuring the tumor environment and inflammatory responses around the tumor. Therefore, I think that the imaging modalities that will allow us to more directly image the cancer cells themselves will be important advancements

in the near future. These may include novel PET-labeled images, quantitative measures by MRI, and other strategies. I think these will especially become important as we develop strategies that target certain components of the tumor and not others.

Another interesting nonradiographic modality for identifying metastatic CRPC that has not really been explored is the use of circulating tumor cells. These cells may be shown to offer a more sensitive, reliable, and quantitative measurement of metastasis, and they may also act as a way to ascertain a patient's response to treatment.

**Daniel W. Lin, MD** Do you use other secondary hormonal strategies in CRPC patients in order to decrease serum testosterone levels to below 50 ng/mL and make sure that they stay below 50 ng/mL?

**Daniel J. George, MD** At this point in time, I have not really focused on this in my practice largely because the therapies we have used to add to primary ADT have been relatively modest in their clinical efficacy. Therefore, it has been difficult to draw any kind of correlation between these relatively low testosterone levels and response to treatments. This may change in the future as we develop more robust targeted therapies.

**Philip W. Kantoff, MD** I agree. I do measure serum testosterone levels when a patient becomes castration-resistant, although historically there have been very few options in the event of non-castrate levels. It has not been my practice to change the secondary hormonal therapy in these cases. Additionally, in light of mounting evidence showing the high levels of tumor-produced androgens even in the presence of serum castrate levels, serum androgen determinations are likely not going to be relied upon heavily in the future. Now, with the introduction of novel agents that will target these residual androgens, we will have to have some type of surrogate marker in order to determine what is actually going on in the tumor.

**Daniel J. George, MD** There has been a major landscape change in CRPC with the recent introduction of novel agents demonstrated to prolong patient survival. What is the rationale for treating patients with these therapies in sequence? Is there any added benefit for treating patients with more than 1 of these agents?

**Philip W. Kantoff, MD** I think that this is a critical question, especially in light of the past year, and the availability of several novel agents for our CRPC patients. Until the proper studies have been performed, I do not have a definitive answer. Overall, my current thinking is that our rationale for using bone-targeted agents should

not change. In some ways, I think the more pressing question is how these strategies should be best sequenced.

I still perceive chemotherapy as an agent or agents for patients who are symptomatic. This is because of all the agents that have now been demonstrated to improve patient survival, chemotherapy carries with it the most significant impact on quality of life. In my mind, the ideal patient for sipuleucel-T is one with documented metastases and indolent disease, as this is the patient population that has thus far been included in clinical trials. With regard to abiraterone, we are limited by FDA guidelines to waiting to initiate treatment following chemotherapy failure. After docetaxel, a choice will have to be made to treat the patient with abiraterone or cabazitaxel; in most circumstances, I would first choose abiraterone due to its lower toxicity.

**Daniel J. George, MD** Should you consider the issue of timing with prednisone treatment and sipuleucel-T administration?

**Philip W. Kantoff, MD** This question is especially important in light of the fact that many patients treated with abiraterone receive concurrent prednisone, due to an abiraterone-induced drop in cortisol levels that causes a compensatory increase in ACTH and in turn an increase in mineralocorticoid activity, resulting in hypokalemia and hypertension. However, there are many patients who would likely do well on abiraterone without concurrent prednisone or with lower-dosage prednisone, and this is an area that needs to be explored.

The concern regarding prednisone therapy proximal to sipuleucel-T is theoretical, as it has not been directly studied. In the IMPACT trial, patients were required to have not been on a steroid for at least 1 month prior to sipuleucel-T treatment.

**Daniel J. George, MD** The results of the IMPACT trial also showed that the immunologic response was associated with survival, although the study was not specifically powered to assess this. It is not known whether concomitant steroid use would affect that immunologic response and, if so, by how much.

**Philip W. Kantoff, MD** We also do not know at what point it would be safe to use a steroid after giving sipuleucel-T.

**Daniel J. George, MD** Another major gap in this field that is becoming increasingly important going forward is a tumor registry. This would help to characterize the natural history of all states of CRPC and help to identify prognostic factors to understand which patients

are achieving the best natural history and with what sequence. I worry that without a prospectively collected contemporary registry series, it will be difficult for any one clinical trial to completely inform us on what the natural history is.

**Daniel W. Lin, MD** Sipuleucel-T experienced several regulatory hurdles, with the FDA initially expressing skepticism about the strength of the data. In your opinion, do you view this drug as having confirmed efficacy for CRPC, or does lingering doubt remain in the physician community?

**Daniel J. George, MD** I think the reality is that we have probably had more FDA scrutiny of these 3 clinical trials, and particularly the pivotal IMPACT study, than almost any other study in oncology. The FDA has done a thorough job in evaluating the patient population, the randomization, the stratification, and the criteria used to select these patients, as well as the clinical outcome associated with this treatment. However, even after intense review, the conclusion remains that these data are valid and are worthy of full approval. Ultimately, the treatment of patients who meet that FDA label should be covered by Medicare and by the vast majority of private insurance payers.

To me, as a physician within the oncology community, there has been very strong validation that these results are really beneficial to patients. In addition to the multitude of peer-reviewed publications and presentations, the additional layer of regulatory scrutiny that these data have passed through is significant, and I certainly feel comfortable explaining this to my patients. I think it is sometimes difficult when we do not have an immediate

anecdotal experience of clinical benefit to rely on when discussing a new treatment with our patients. However, in asymptomatic patients, prostate cancer response is very difficult to measure by traditional measures of disease burden, and even PSA levels have their limitation. I am comfortable with the fact that we have not yet characterized how best to interpret a response to sipuleucel-T, and I remain confident that in the future we will be able to identify those patients who are going to benefit most from treatment, and thus enrich our populations.

**Philip W. Kantoff, MD** I completely agree. I think that the first question is the validity of the body of work, which has been established. The difficulty with this therapy is that it represents a new paradigm, and it is difficult to explain in terms of mechanism of action. The issue is how does it work and how does it provide clinical benefit? In the absence of seeing a measurable decline in tumor burden in patients, evidenced by decreased PSA levels and reduced tumor size, it is difficult for oncologists to remain confident in the treatment, especially with a lack of delayed time to progression. I think for the most part, the community has moved beyond the issue of “is it true?” and instead is moving into the realm of “how does it work?”

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# Slide Library

## Traditional Treatments of Metastatic CRPC

Until recently, the only treatment strategies available for patients with metastatic CRPC have been:

- Secondary hormonal therapy (including the antiandrogens [nilutamide, flutamide, and bicalutamide] and androgen-suppressing agents [ketoconazole and estrogen])
- Traditional chemotherapeutics (docetaxel or mitoxantrone plus prednisone, and estramustine)
- Supportive care measures (bisphosphonates, erythropoietin, and palliative care agents)

CRPC=castration-resistant prostate cancer.

## Clinical Subtypes of Metastatic CRPC

The Prostate Cancer Clinical Trials Working Group has defined clinical subtypes of metastatic CRPC based on pattern of disease spread. These subtypes include:

- Locally progressing tumors with no evidence of metastasis
- Rising PSA levels with no evidence of metastasis
- Nodal spread with no detectable bone or visceral (lung or liver) metastasis
- Bone disease with or without nodal spread and no detectable visceral metastasis
- Visceral metastasis with or without spread at other sites

Data from Cowher HJ et al. J Clin Oncol. 2008;26:1148-1155.

## Sipuleucel-T

The individualized dendritic cell vaccine sipuleucel-T represents the first FDA-approved agent in a novel immunotherapeutic class of agents.

- The treatment begins with leukapheresis to isolate peripheral blood mononuclear cells
- Antigen-presenting cells, including dendritic cells, are then activated by exposing the peripheral blood mononuclear cells to a PMP-GM-CSF recombinant protein fusion conjugated of the prostatic acid phosphatase (PAP) fused with human granulocyte-macrophage colony-stimulating factor (GM-CSF)
- These treated cells are then reinfused into the patient
- The entire process (leukapheresis and in vitro PMP-GM-CSF treatment followed by reinfusion) is repeated every 2 weeks for a total of 3 treatments

FDA/US Food and Drug Administration.

## Results of the Phase III IMPACT Trial

- A trial of 512 patients with either asymptomatic or minimally symptomatic metastatic CRPC. Patients were randomized in a 2:1 ratio to receive either sipuleucel-T or placebo<sup>1</sup>
- Compared with the placebo arm, patients in the sipuleucel-T arm achieved a 22% relative reduction in the risk of death. This reduction represented a 4.1-month increase in median OS between the placebo and sipuleucel-T arms
- The rate of 3-year OS was also increased with sipuleucel-T compared with placebo
- There was no significant difference achieved in the PSA response or time to progression between the 2 treatment arms
- Sipuleucel-T treatment was well tolerated

1. Kantoff PW et al. N Engl J Med. 2010;362:111-120.  
IMPACT=Immunotherapy Prostate Adjuvantive Treatment; OS=overall survival; PSA=prostate-specific antigen.

## Abiraterone Acetate

- Standard initial therapy for advanced prostate cancer
- Approved by the FDA for the treatment of metastatic CRPC following progression on docetaxel therapy
- Many patients ultimately develop CRPC, evidenced as disease progression in the setting of castrate serum levels of testosterone
- In a phase III trial of abiraterone vs placebo, abiraterone achieved improved median OS, time to PSA progression, and radiographic PFS. A greater proportion of abiraterone patients achieved a PSA response<sup>1</sup>

1. de Bono J et al. 36th European Society of Medical Oncology (ESMO) Meeting, October 8-12, 2010, Nice, France. Abstract LBA400=overall survival; PFS=progression-free survival.

## Denosumab

- Denosumab is a monoclonal antibody directed against the receptor activator of the nuclear factor  $\kappa$ B ligand (RANKL). Denosumab inhibits the bone resorption function of osteoclasts and thus delays bone destruction
- The FDA approved denosumab for the prevention of skeletal-related events in patients with bone metastases from solid tumors
- In a phase III trial of denosumab vs placebo, denosumab increased bone mineral density of the total hip, femoral hip, and distal third of the radius<sup>1</sup>
- In a phase III trial of denosumab vs zoledronic acid, median time to first skeletal-related event was prolonged in the denosumab arm<sup>2</sup>

1. Smith MR et al. N Engl J Med. 2009;361:746-756.  
2. Fizazi K et al. Cancer. 2011;117:1933-40.

## Cabazitaxel

- Novel tubulin-binding microtubule inhibiting agent
- FDA-approved for the second-line treatment of patients with advanced hormone-refractory prostate cancer following docetaxel treatment
- In a phase III trial of cabazitaxel vs mitoxantrone (both administered with prednisone), the cabazitaxel patients achieved prolonged median OS, increased PFS, and higher response rates<sup>1</sup>

1. de Bono J et al. Lancet. 2010;376:1147-1154.

## Inhibiting the Interaction Between Androgens and the Androgen Receptor

### Novel Agents

- MDV3100 inhibits the subsequent translocation of the androgen receptor complex to the nucleus, thereby preventing downstream activation of the androgen receptor-responsive pathways
- TAK-700 is an orally available, selective nonsteroidal androgen synthesis inhibitor. TAK-700 exerts its action by specifically targeting CYP17, a key enzyme involved in the production of DHEA

## Novel Targeted Agents

- OGX-11 is an inhibitor of the clusterin protein, a cytoprotective chaperone protein that acts similarly to heat shock proteins
- XL-184 is a potent inhibitor of both the MET and the vascular endothelial growth factor receptor 2 pathways involved in proliferation and angiogenesis

## Novel Immunotherapeutics

Based on the success of the immunotherapy agent sipuleucel-T, several other immunotherapeutic approaches are under investigation in metastatic CRPC. Examples include:

- Passive immunotherapy (the transfer of monoclonal antibodies or other immunologic agents)
- Active immunotherapy (vaccines)
- Gene therapy

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