

Challenges in Treating Advanced Disease

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Abstract

Castration-resistant prostate cancer (CRPC) has historically presented significant challenges to both clinicians and patients in regard to disease progression and consequent management. The first advances in the treatment of this state of prostate cancer with docetaxel chemotherapy demonstrated a survival benefit over the palliative standard of care, mitoxantrone combined with prednisone. The recognition that these patients still maintained active androgen receptor access identified new therapeutic agents for CRPC that aimed to further deplete testosterone levels or directly interact with the androgen receptor (ie, enzalutamide). Other therapeutic targets that have established efficacy in randomized phase 3 trials include bone metastases (ie, radium 223 dichloride), the immune system (ie, sipuleucel-T), and tubulin (ie, cabazitaxel). These new and evolving agents are positioned to substantially alter the therapeutic environment for CRPC and to improve patient outcomes and quality of life.

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For author information and disclosures, see end of text.

Management of Castration-Resistant Prostate Cancer: Where Have We Been and Where Are We Going?

While patients with localized prostate cancer (PrCa) may have the disease eradicated with local treatments such as radical prostatectomy or radiation therapy (RT), the treatment of advanced disease involves systemic therapy such as androgen blockade, chemotherapy, and isotope therapy. Androgen deprivation therapy (ADT) with a luteinizing-hormone-releasing hormone (LHRH) agonist or antagonist is typically administered as first-line therapy.¹ Unfortunately, progression of disease after initial response to androgen blockade (termed castration-resistant prostate cancer or CRPC) is heterogeneous, and is marked by any or all of the following criteria: (1) rising PSA; (2) progression of bone metastases; or (3) progression of visceral or soft tissue lesions. This disease progression occurs despite castrate levels of testosterone (≤ 50 ng/mL).¹⁻⁴ Patients may also present for the first time with castration-resistant disease, although fewer than 5% of men diagnosed with PrCa initially present with evidence of metastases.¹

The prognosis for patients with CRPC is heterogeneous and is related to numerous clinical factors, such as pain, weight loss, performance status, and markers related to the extent of disease, such as hemoglobin, lactate dehydrogenase (LDH), alkaline phosphatase, and the sites of disease.⁵ However, investigational trials over the past 20 years have revolutionized therapy for CRPC. Research has led to the discovery and further advancements of a select group of chemotherapies, hormonal treatments, immunotherapies, and palliative agents that have been approved by the US Food and Drug Administration (FDA) for use in patients with CRPC, and some therapies have been shown to improve survival. Other therapies are still undergoing investigation in preclinical and clinical trials to continue the discovery of optimal treatment regimens that will delay disease progression, maximize patient survival time, and minimize side effects to improve clinical outcomes and quality of life (QOL) in patients with advanced, castration-resistant disease.¹

In May 2013, the American Urological Association (AUA) published an updated classification system that identified 6 types of “index patients” with CRPC to serve as a basis for treatment decisions. These 6 index patients were believed to represent the most common clinical scenarios encountered in practice for managing patients with CRPC. These patient models were created

with variations that depend upon the presence or absence of metastases, degree of symptoms, performance status, and prior treatment with “standard of care” docetaxel-based chemotherapy or lack thereof:

1. Asymptomatic non-metastatic CRPC
2. Asymptomatic or minimally symptomatic metastatic CRPC (mCRPC) with no prior docetaxel therapy
3. Symptomatic mCRPC with good performance status and no prior docetaxel therapy
4. Symptomatic mCRPC with poor performance status and no prior docetaxel therapy
5. Symptomatic mCRPC with good performance status and prior docetaxel therapy
6. Symptomatic mCRPC with poor performance status and prior docetaxel therapy

The overriding goal of this guideline update was to provide classifications for evidence-based recommendations for the treatment of patients with CRPC, allowing for better individualization of management strategies for castration-resistant disease.⁷ However, CRPC is a biologically heterogeneous disease, and evidence is not yet sufficient to formulate appropriate guidance for therapy based on individual tumor biology.

Systemic Chemotherapy in CRPC: Evolving Standards of Care

Numerous phase 2 clinical trials have evaluated single-agent chemotherapy for CRPC, including agents from drug classes such as the anthracyclines, alkylating agents, antimetabolites, platinum-based agents, and topoisomerase inhibitors.⁸⁻¹⁰ An analysis of 26 trials that assessed various chemotherapies (prior to the advent of routine PSA assessment used to gauge treatment effectiveness) found that the response rate, defined as patients who achieved complete or partial response according to National Prostate Cancer Project criteria, exceeded 10% in 6 of the 26 trials and averaged 8.7% (95% confidence interval [CI], 6.4%-9.0%) in patients with CRPC treated with single-agent therapy.¹⁰ The combination of mitoxantrone plus prednisone was the only chemotherapeutic option for patients with CRPC, and has been found to provide palliative benefits with reductions in pain and improved QOL.^{1,11} This practice pattern shifted when docetaxel plus prednisone or docetaxel plus estramustine became the leading combinations as the evidence-based standard in chemotherapy, and the first-line treatment for castration-resistant disease. Another novel agent, cabazitaxel, has been studied and approved for second-line chemotherapy after failure of docetaxel-based chemotherapy in patients with mCRPC.^{1,8}

Docetaxel

Docetaxel is a taxane chemotherapeutic agent that induces the polymerization of microtubules and phosphorylation of the Bcl-2 protein.⁵ The results of 2 ground-breaking randomized controlled trials established the role of docetaxel in treating CRPC, demonstrating the survival benefit in patients who had received this agent.¹ The TAX 327 study evaluated 1006 men who were assigned to receive prednisone 5 mg with either docetaxel (75 mg/m² of body surface area every 3 weeks, or 30 mg/m² weekly for 5 of 6 weeks) or mitoxantrone (12 mg/m² every 3 weeks). Results of TAX 327 demonstrated that the patients who received docetaxel 75 mg/m² every 3 weeks had a median survival of 18.9 months versus 16.5 months for those who had received mitoxantrone. Survival for those in the weekly docetaxel cohort was also higher than that seen for patients who received mitoxantrone (median survival of 17.4 months). Patients who had received docetaxel experienced significantly higher rates of decreasing serum PSA levels, with 45% of those receiving docetaxel every 3 weeks and 48% of those on the weekly regimen encountering at least a 50% decrease in serum PSA compared with 32% of patients who had received mitoxantrone ($P < .001$ for both). The study also demonstrated higher rates of response in terms of improving pain and QOL in the docetaxel cohorts.^{1,12} Using data that had been collected between 2003 and 2007, a longer-term analysis confirmed the survival benefit demonstrated in TAX 327: a median survival of 19.2 months was seen in patients who had received docetaxel every 3 weeks versus 17.8 months in the docetaxel weekly group and 16.3 months in the mitoxantrone treatment cohort.¹³

Similar results were seen in the SWOG-9916 study, which had assigned 770 men to 1 of 2 treatment arms given in 21-day cycles. Participants received either 280 mg of estramustine taken 3 times daily for days 1 to 5 of the 21-day cycle, and a single 60 mg/m² dose of intravenous (IV) docetaxel on day 2 (with dexamethasone premedication) or 12 mg/m² of IV mitoxantrone on day 1 with twice-daily dosing of 5-mg prednisone. Doses were later escalated in patients who were able to tolerate initial chemotherapeutic doses without grade 3 or 4 adverse events. In the intent-to-treat analysis, the median overall survival was 17.5 months in those who had received combination therapy with docetaxel versus 15.6 months in patients in the mitoxantrone treatment arm ($P = .02$). The median time to progression of disease was 6.3 months in patients who had received docetaxel versus 3.2 months in patients who had received mitoxantrone ($P < .001$). The percentage of patients with reductions in PSA of 50% or more was higher among the patients who had been

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treated with docetaxel than in patients who had been treated with mitoxantrone (50% vs 27%; $P < .001$). Pain relief was similar in both groups, although significantly higher rates of side effects were seen in the docetaxel treatment cohort (ie, grade 3 or 4 neutropenic fevers [$P = .01$], nausea/vomiting [$P < .001$], cardiovascular events [$P = .001$]).^{11,14}

In 2007, a prognostic model using baseline variables from participants in the TAX 327 study was created to predict mortality among patients with CRPC. Using 11 variables among a patient's cancer parameters (eg, treatment, liver metastases, number of metastatic sites, pain, performance status, disease progression, tumor grade, alkaline phosphatase, PSA, PSA doubling time, and hemoglobin), the model was designed to foster a clinician's ability to estimate survival duration. This multivariate model identified new independent prognostic factors in men with metastatic CRPC (mCRPC), including PSA doubling time. A prognostic tool such as this may help to provide additional individualized management for patients with CRPC, and may have a larger role in the future as new therapies emerge and are approved for use in castration-resistant disease.¹⁵

Cabazitaxel

Cabazitaxel was the third chemotherapeutic agent approved by the FDA for use in patients with CRPC.¹⁶ This agent is also an inhibitor of microtubule depolymerization; however, unlike docetaxel, it is resistant to P-glycoprotein that is often expressed in malignant cells.¹ Studies have demonstrated cabazitaxel activity in patients with CRPC who were previously treated with docetaxel. The phase 3 trial TROPIC demonstrated the efficacy of cabazitaxel in men with castration-resistant disease who had been previously treated with docetaxel. This was not purely a second-line chemotherapy trial, as 25% of patients had 2 or more prior chemotherapies. TROPIC randomized 755 men with progressive mCRPC to either cabazitaxel 25 mg/m² or mitoxantrone 12 mg/m² plus daily prednisone. Median survival was 15.1 months in patients treated with cabazitaxel versus 12.7 months among participants from the mitoxantrone treatment cohort. During the trial, the risk of death was significantly lower in patients treated with cabazitaxel versus patients treated with mitoxantrone (hazard ratio [HR], .70; 95% CI, .59-.83; $P < .0001$). However, a higher death rate within 30 days of receiving the last dose of chemotherapy was observed in patients who had been treated with cabazitaxel compared with those treated with mitoxantrone (5% vs 2%, respectively). Higher rates of side effects, including febrile neutropenia, diarrhea, nausea/vomiting, anemia, and thrombocytopenia, were observed in the patients in the cabazitaxel

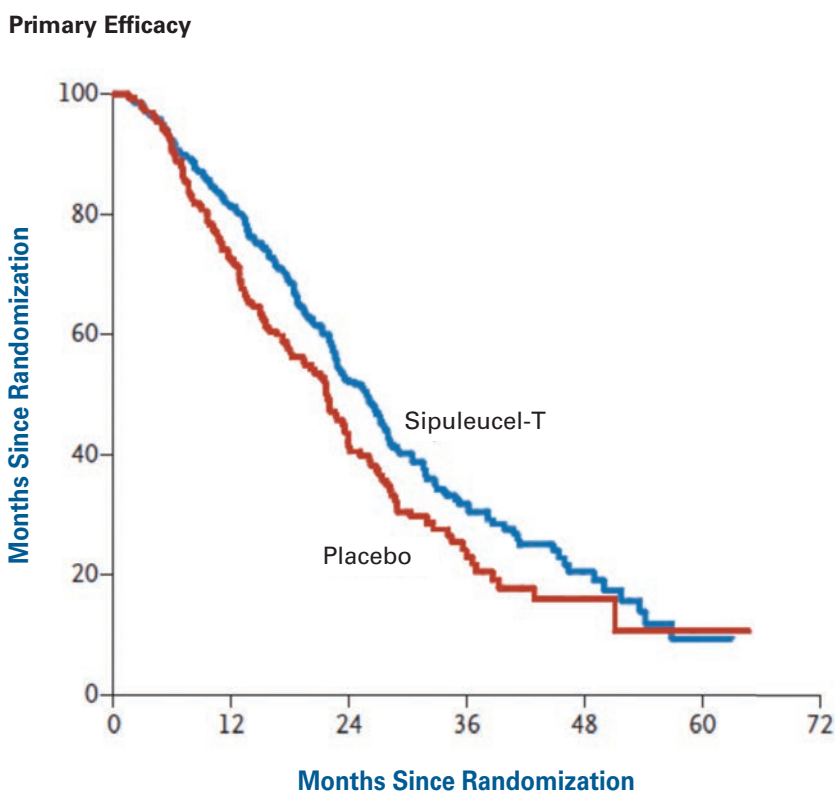
group. These patients had a higher risk of death within 30 days of the last cabazitaxel administration, which may be attributed to neutropenia, which was seen in 94% of patients who had received cabazitaxel, with 82% of cases at grade 3 neutropenia or higher. Febrile neutropenia occurred in 8% of patients treated with cabazitaxel compared with 1% of patients treated with mitoxantrone. This finding portends the need for extra vigilance on the part of clinicians, including further treatment or prophylaxis to prevent neutropenia in patients at risk.^{17,18} Randomized trials are now evaluating whether 20 mg/m² of cabazitaxel every 3 weeks has similar efficacy to the approved dosage of 25 mg/m² every 3 weeks, but with less toxicity.¹⁹ An international randomized trial comparing cabazitaxel 25 mg/m² or 20 mg/m² combined with prednisone to the standard docetaxel/prednisone combination as first-line therapy is also currently under way.^{1,20} It should be noted that in 2010, cabazitaxel was approved by the FDA for use in men with mCRPC who prove refractory to docetaxel therapy.^{1,17,18}

Immunotherapy in CRPC: Sipuleucel-T

Immunotherapy is a form of biological therapy that utilizes the host immune system to either delay or stop the growth of malignant cells by targeting tumor-associated antigens (TAAs) or disrupting molecular growth pathways.²¹ One immunotherapeutic approach involves the use of therapeutic cancer vaccines that are designed to elicit antitumor T-cell responses.²¹ Sipuleucel-T is designed to stimulate T-cell immunity against prostatic acid phosphatase, which is unique to the surface of most PrCa tumor cells.^{1,22} Sipuleucel-T is composed of autologous peripheral blood mononuclear cells (PBMCs) that have been activated *ex vivo* with a recombinant fusion protein termed PA2024, which contains prostatic acid phosphatase fused to granulocyte-macrophage colony-stimulating factor and serves as an immune cell activator.²³ Combined data from 2 initial phase 3 clinical trials of sipuleucel-T in patients with mCRPC demonstrated that the median survival for patients on this agent improved significantly by 4.3 months (23.2 months vs 18.9 months; $P = .011$) compared with those who were treated with placebo. It should be noted, however, that no significant difference in time to disease progression was found between the 2 cohorts (11.1 weeks for sipuleucel-T vs 9.7 weeks for placebo; $P = .111$).^{1,22,24}

To confirm the improvements seen in survival in the first 2 randomized trials, the IMPACT trial randomly assigned 512 patients to receive either sipuleucel-T or placebo, administered intravenously every 2 weeks for 3 total infusions. Patients entered into the study were

■ **Figure 1.** Sipuleucel-T/Placebo Kaplan Meier Estimates of Overall Survival²³



No. at Risk						
Sipuleucel-T	341	274	129	49	14	1
Placebo	171	123	55	19	4	1

From *The New England Journal of Medicine*, Kantoff PW, Higano CS, Shore ND, et al, Sipuleucel-T immunotherapy for castration-resistant prostate cancer, 363:411-422. Copyright © 2010 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

asymptomatic or minimally symptomatic, and could not have visceral disease. Prior chemotherapy in patients was permitted; however, those treatments needed to have been completed at least 3 months prior to entry into IMPACT. The results demonstrated a relative reduction of 22% in the risk of death in the sipuleucel-T group compared with participants who had received placebo. This reduction signified a 4.1-month median survival improvement for those in the sipuleucel-T cohort. Median survival was 25.8 months for patients who had received sipuleucel-T versus 21.7 months for patients who had received placebo (Figure 1).²³ The probability for survival over 36 months was estimated to be 31.7% in the sipuleucel-T treatment group versus 23.0% in the placebo cohort. Time to disease progression was similar for both study groups, as seen in the earlier sipuleucel-T trials. The discordance in disease progression and overall survival may be attributed to a delayed or prolonged activation of the immune system.²³ IMPACT confirmed the previous finding that sipuleucel-

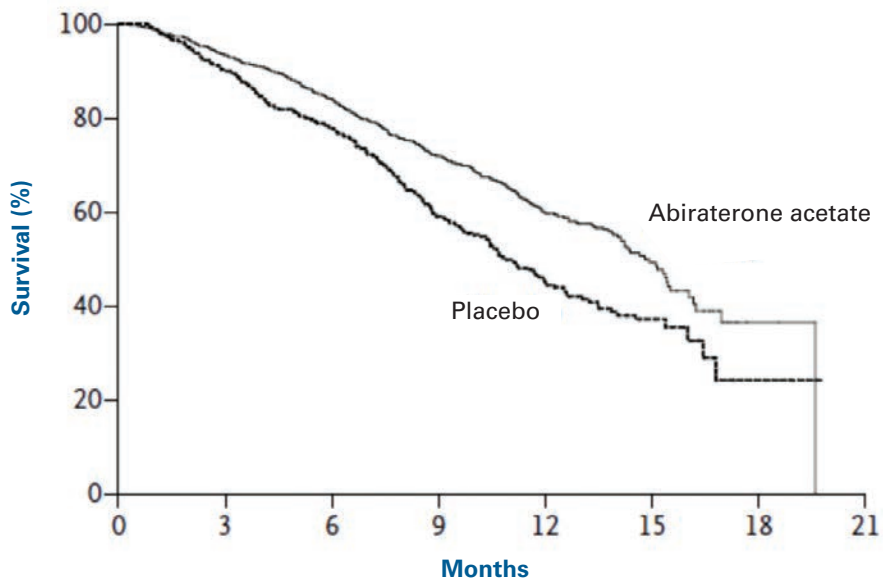
T prolonged overall survival in men with mCRPC.^{1,23} With these data, sipuleucel-T became the first autologous immunotherapy approved by the FDA for use in treatment in any cancer in 2010.¹

Molecularly Targeted Therapies in CRPC: The New Frontier

Through research over the past few decades, investigators have acknowledged that despite the fact that most men with PrCa eventually fail ADT, most of these tumors maintain some dependence on androgen and/or androgen receptor (AR) signaling for tumor proliferation and disease progression. In addition, androgen independent molecular pathways have also been identified as culprits in the progression to CRPC. With these findings, new agents that specifically target new pathways have been developed and continue to emerge to provide an even greater armamentarium against disease progression in CRPC and improvement of outcomes and patient QOL.²⁵

■ **Figure 2.** Abiraterone Acetate/Placebo Kaplan Meier Estimates of Overall Survival²⁷

Overall Survival



No. at Risk								
Abiraterone acetate	797	736	657	520	282	68	2	0
Placebo	398	355	306	210	105	30	3	0

From *The New England Journal of Medicine*, Bono JS, Logothetis CJ, Molina A, et al, Abiraterone and increased survival in metastatic prostate cancer, 364:1995-2005. Copyright © 2011 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

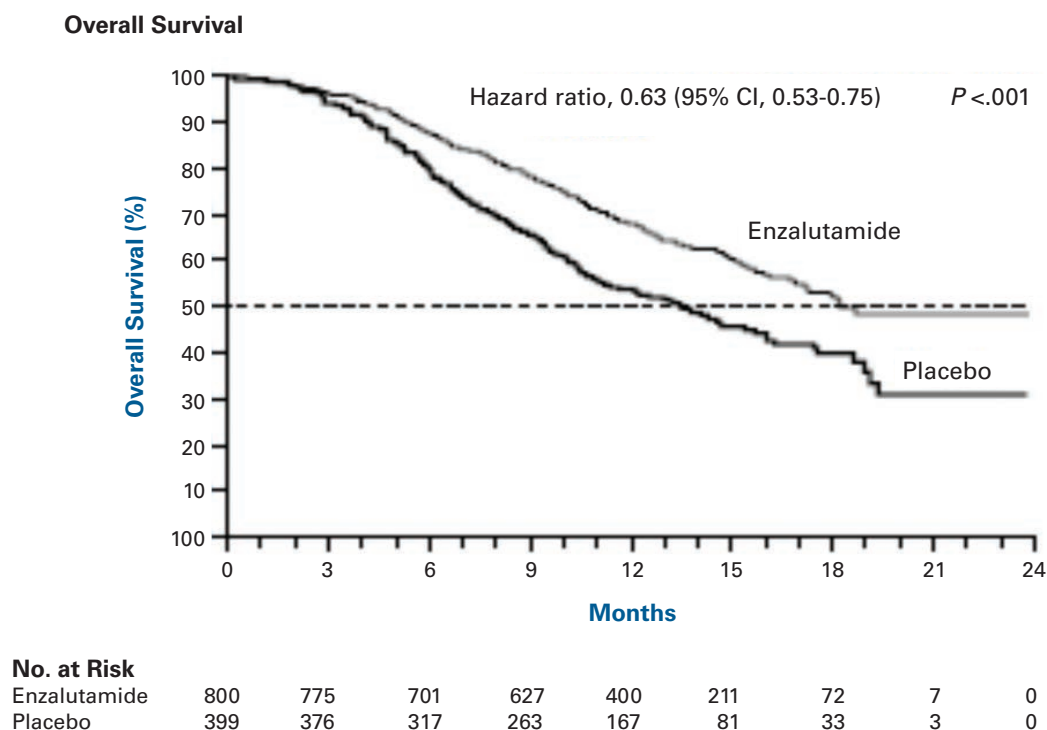
Abiraterone Acetate

Abiraterone acetate is an analogue of pregnenolone; the compound and its metabolite, abiraterone, are both highly selective, potent, irreversible inhibitors of CYP17. The main target of this agent is C17, 20-lyase, which is necessary for the androgen production that leads to PrCa cell proliferation.^{1,25,26} Abiraterone acetate has been evaluated in both the pre-and post docetaxel settings.^{1,27} In the COU-AA-301 study, 1195 patients who had progressed after therapy with docetaxel were randomized on a 2 to 1 basis to either abiraterone acetate 1000 mg once daily/prednisone 5 mg twice daily or placebo/prednisone 5 mg twice daily. A significantly longer median survival of 14.8 months was demonstrated in patients who had received abiraterone acetate versus 10.9 months for patients in the placebo group ($P < .001$). (Figure 2).²⁷ Secondary end points, including time to progression of PSA (10.2 months for abiraterone acetate vs 6.6 months for placebo; $P < .001$), progression-free survival (5.6 months vs 3.6 months, respectively; $P < .001$), and PSA response rate (29% vs 6%, respectively; $P < .001$) clearly demonstrated the significantly more favorable impact of abiraterone acetate therapy. It should be noted that mineralocorticoid-related side effects, including fluid retention,

hypertension, and hyperkalemia, were seen more often in the abiraterone acetate–treated patients.²⁷

The use of abiraterone acetate is now undergoing study in patients without previous chemotherapy. The COU-AA-302 study randomized 1088 patients who had not received previous chemotherapy to either abiraterone acetate 1000 mg plus prednisone 5 mg daily or placebo plus prednisone. Primary end points included radiographic progression-free survival and overall survival. This particular study was unblinded following a planned interim analysis after 43% of expected deaths had occurred. Median radiographic progression-free survival was 16.5 months in the abiraterone acetate cohort versus 8.3 months in patients who had received the placebo/prednisone combination. After a median 22.2 months of follow-up, overall survival improved but did not cross the efficacy end point for patients who had received abiraterone acetate; in these patients, the median was not reached when compared with 27.2 months for those who had received placebo/prednisone. Abiraterone acetate/prednisone demonstrated superiority over prednisone alone regarding time to initiation of cytotoxic chemotherapy, use of controlled pain medications, PSA progression, and decline in performance status.²⁸ This study led to the approval of abiraterone acetate

■ **Figure 3.** Enzalutamide/Placebo Kaplan Meier Estimates of Overall Survival³³



From *The New England Journal of Medicine*, Scher HI, Fizazi K, Saad F, et al, Increased survival with enzalutamide in prostate cancer after chemotherapy, 367,1193. Copyright © 2012 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

for use prior to docetaxel chemotherapy.²⁹ Factors which may explain why survival benefit has yet to be achieved in this clinical state include crossover to abiraterone in studies, as well as the plethora of subsequent treatments that the patients may also receive.^{1,28}

Enzalutamide

Enzalutamide (previously known as MDV3100) is a small molecule AR antagonist which acts by blocking nuclear translocation and coactivator recruitment. This agent also prevents DNA binding, induces cellular apoptosis, and does not demonstrate AR agonist activity in situations of AR overexpression.^{1,30} When compared with bicalutamide, enzalutamide has a 5- to 8-fold greater affinity for the AR.¹ Enzalutamide has also been shown to lower PSA, suppress tumor growth, and induce cellular apoptosis in human PrCa cell lines.^{1,31} This agent was approved by the FDA in August 2012 for use in patients with mCRPC who have been previously treated with docetaxel.³² This approval was based upon the results of the AFFIRM study, a phase 3 trial which assessed 1199 men with CRPC and progressive disease, post docetaxel chemotherapy.^{32,33} Participants were randomized to receive either oral enzalutamide 160 mg or pla-

cebo. Corticosteroids were used by 48% of patients receiving enzalutamide and 46% of patients receiving placebo. Overall survival was the primary end point of the study, but the trial was halted after a planned interim analysis at the time of 520 deaths. Median overall survival was 18.4 months in the patients who had received enzalutamide versus 13.6 months for those in the placebo group (Figure 3).³³ Enzalutamide demonstrated superiority over placebo for all secondary end points (Table).³³

Rates of some of the side effects experienced, such as fatigue, diarrhea, and hot flashes, were higher in patients who had received enzalutamide. However, seizures were reported in 5 of 800 patients (0.6%) treated with enzalutamide and none of the patients in the placebo arm.³³ It should be noted that patients with a history of seizures were excluded from the trial, and the FDA has documented that the safety of this agent in patients with histories of seizures is unknown. It should be also noted that enzalutamide does not require concomitant administration of prednisone and is administered orally versus the need for infusions as needed with other agents for the treatment of CRPC.²⁷ In fact, a retrospective post hoc analysis of the patients who were on corticosteroids at entry to AFFIRM, independent of other

■ **Table.** AFFIRM Study: Secondary End Points Achieved, Enzalutamide vs Placebo Cohorts³³

Secondary Endpoint	Patients/Time (Enzalutamide)	Patients/Time (Placebo)
Reduction in PSA \geq 50%	54%	2%
Soft-tissue response rate	29%	4%
QOL response rate	43%	18%
Time to PSA progression	8.3 months	3.0 months
Radiographic PFS	8.3 months	2.9 months
Time to first SRE	16.7 months	13.3 months

PFS indicates progression-free survival; PSA, prostate-specific antigen; QOL, quality of life; SRE, skeletal-related event. From *The New England Journal of Medicine*, Scher HI, Fizazi K, Saad F, et al, Increased survival with enzalutamide in prostate cancer after chemotherapy, 367,1193. Copyright © 2012 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

prognostic factors, demonstrated a poorer survival compared with those patients who were not on steroids.³⁴

Bone Health in mCRPC

PrCa is especially prone to metastatic spread, and bone is the most common site for metastases, most often manifesting within the spine, followed in frequency by the pelvis, hip, femur, and skull.³⁵ Bone metastases are associated with pain, pathologic fracture, spinal cord compression, and lowered survival in patients with CRPC. As such, several different classes of therapy with various mechanisms of action have been tested and utilized in patients with metastatic disease in efforts to combat the substantial burden of bone-related disease and skeletal-related events.^{1,36}

Zoledronic Acid

Therapies that target bone for mCRPC have mostly been limited to drugs that delay skeletal-related events (SREs). Zoledronic acid is a nitrogen-containing bisphosphonate that targets osteoclasts and prevents bone reabsorption.³⁷ Pivotal data assessing zoledronic acid in 2 dosages (4 mg IV every 3 weeks [n = 214] or 8 mg IV every 3 weeks [n = 221]) versus placebo (n = 208) demonstrated that, over 15 months, patients with mCRPC who had received placebo showed a greater proportion of SREs compared with those who had received either of the dosages of zoledronic acid. Median time to the first SRE was 321 days for patients who had received placebo, was not reached for those receiving zoledronic acid 4 mg, and was 363 days for patients who had received the higher test drug dose. The lower dosage was well tolerated when given as a 15-minute infusion, but the 8-mg dose was associated with renal dysfunction. The study concluded that zoledronic acid at 4 mg reduced SREs in patients with mCRPC.^{1,37} Long-term evaluation of the 122 patients who had completed treatment with 24 months of the 4-mg dose against placebo provided similar results: those who had received zoledronic acid experienced a median of 488 days to the first SRE versus 321 days

in the placebo group ($P = .009$). The data demonstrated the safety of the drug and its potential long-term clinical benefits in men with mCRPC at risk for SREs.³⁸

Denosumab

Another therapy that has demonstrated efficacy in reducing SREs in men with CRPC is denosumab, a fully human monoclonal antibody administered subcutaneously. Denosumab blocks the RANK ligand (RANK-L) associated with metastatic disease, acting by preventing bone resorption through osteoclast activation in bone.^{1,39} In 1 study that compared denosumab 60 mg dosed every 6 months with placebo in men undergoing ADT, bone mineral density within the lumbar spine increased by 5.6% in the denosumab group compared with the 0.1% loss of bone density in the placebo group ($P < .001$). Denosumab was associated with significant increases in bone mineral density in the other indices measured (ie, total hip, femoral neck, distal third of the radius) throughout the course of the study. Patients who had received denosumab experienced a decreased incidence of new vertebral fractures at 36 months (1.5% compared with 3.9% of those who received placebo), but rates of adverse events were similar between the treatment and placebo cohorts.⁴⁰

In a study of 1432 men with non-metastatic CRPC, patients who had received denosumab 120 mg administered every 4 weeks experienced increased bone-metastasis-free survival by a median of 4.2 months over placebo (29.5 months vs 25.2 months, respectively; HR 0.85; $P = .028$). Denosumab also significantly delayed time to the initial appearance of bone metastases compared with placebo (33.2 months vs 29.5 months, respectively; HR 0.84; $P = .032$). Overall survival did not differ between the treatment cohorts, and rates of adverse events were similar.⁴¹

Another landmark trial that assessed denosumab versus zoledronic acid included 1904 men with CRPC and no previous exposure to IV bisphosphonate therapy. A total of 950

patients were randomized to denosumab and 951 to receive zoledronic acid. The primary end point was time to first SRE during the study. Median time to first on-study SRE was 20.7 months for patients who had received denosumab versus 17.1 months for those randomized to zoledronic acid ($P = .008$ for superiority of denosumab). The study results demonstrated that denosumab proved better than zoledronic acid for the prevention of SRE in CRPC, with similar rates of adverse events between the 2 treatment cohorts.⁴² Clinicians must perform oral/jaw examinations on patients receiving the drug and must also monitor serum calcium levels closely in these patients.¹ One study found that the incidence of osteonecrosis of the jaw (ONJ) was 4% with denosumab use after 3 years of follow-up in patients with CRPC.⁴¹ Another study found that after approximately 1 year of follow-up in patients with CRPC, 2% of patients receiving denosumab versus 1% of patients using zoledronic acid experienced ONJ; however, no significant difference was established between the 2 treatments ($P = .09$).⁴⁰

Radium Ra-223 Dichloride (Ra-223)

Bone-seeking radiopharmaceuticals, such as samarium-153 ethylene diamine tetramethylene phosphonate and strontium-89, have been used for many years to relieve pain from bone metastases in men with mCRPC by utilizing ionizing radiation to kill cancer cells and reduce tumor burden. These drugs act through selective uptake and increased retention at sites of increased osteoblastic activity in bone. In addition to chemotherapy, they provide pain management and reduce the progression of bony metastases; and emerging evidence indicates that some radionuclides may also improve survival time.^{1,43}

In contrast to samarium and strontium, which are beta-emitters, radium dichloride (Ra-223) is a targeted alpha-emitter that acts as a bone-seeking calcium mimetic.^{1,36} The radiopharmaceutical generates localized radiation zones to induce non-reparable, double-stranded DNA breaks in metastatic bone cells without harming normal tissue.^{7,36} This is in contrast to the actions of strontium and samarium, which induce single-stranded DNA breaks that are more easily repaired.⁴⁴ Data from the multicenter, randomized, controlled trial ALSYMPCA in men with mCRPC demonstrated a significant overall survival benefit that favored Ra-223. Patients who had received Ra-223 demonstrated a median overall survival of 14.0 months versus 11.2 months for those who had received placebo (HR 0.695, $P = .00185$). These results led to the early unblinding of the trial, and patients assigned to the placebo cohort were then offered treatment with Ra-223.^{45,46} An exploratory updated analysis

that was conducted later in the trial confirmed the ability of Ra-223 to extend overall survival in patients with mCRPC. These results led to the FDA reviewing Ra-223 under the agency's priority review program. The drug was approved for use in patients with mCRPC in May 2013, as it was viewed to provide a beneficial, safe, and effective therapy when no satisfactory alternative therapy exists, or offer significant improvement compared with currently marketed products.⁴⁷

Other Agents Undergoing Research in CRPC

While current emphasis on the therapeutic landscape for CRPC focuses primarily on the drug agents that have demonstrated survival improvement in CRPC, as noted earlier, a substantial number of other agents and drug classes are currently undergoing investigation in patients with the disease. Particular agents or classes of therapy being researched include^{1,7}:

- TAK-700 (orteronel)—an oral C17, 20-lyase inhibitor
- VT-464—a CYP17A1 protein inhibitor that blocks C17, 20-lyase and 17 α -hydroxylase
- PROSTVAC—a therapeutic PSA-targeted cancer vaccine
- Ipilimumab—a T-cell potentiator that blocks cytotoxic T-lymphocyte antigen-4
- Tasquinomod—an oral antiangiogenesis agent
- XL-184 (cabozantinib)—an oral inhibitor of vascular endothelial growth factor (VEGF) and c-MET
- Custirsen—an inhibitor of clusterin, a protein that is associated with cancer treatment resistance

Another area of research is prostate-specific membrane antigen (PSMA), a cell surface glycoprotein that is expressed by prostate epithelial cells. PSMA-specific monoclonal antibodies that have been identified characterize the function and biodistribution of PSMA, and are a potential target protein for antibody-directed therapy for PrCa, as PSMA expression is mostly restricted to prostate epithelial cells and is over-expressed in patients with PrCa.⁴⁸ With pipeline development proceeding at a rapid pace, emerging and experimental agents aimed at new therapeutic targets promise further changes in the current treatment algorithms for patients with CRPC, offering the potential for improved outcomes and patient QOL.¹ Data surrounding improved survival, however, are still lacking and remain to be quantified.

Where Do We Go From Here? Translating Data Into Actual Clinical Practice

With the identification of the index patients with CRPC that are most often seen in actual clinical practice, the AUA

has created a patient management algorithm that is based on these index presentations, focusing on traditional, approved therapies (ie, antiandrogens such as bicalutamide/flutamide, androgen synthesis inhibitors such as ketoconazole), primary and secondary chemotherapies (ie, docetaxel, cabazitaxel), immunotherapy (ie, sipuleucel-T), and molecularly targeted therapies (ie, abiraterone, enzalutamide), depending on the patient and the disease factors. Further, those treatment pathways are likely to be updated continually as additional data are accumulated and the therapeutic pipeline grows. For example, it should be noted that the algorithm was created and approved prior to the FDA approval of Ra-223 for the treatment of bone metastases in mCRPC and as such do not discuss this agent. To address such inevitable circumstances, the AUA authors provide a disclaimer stating: "This guideline should be used in conjunction with recent systematic literature reviews and an understanding of the individual patient's treatment goals. In all cases, the patient's preferences and personal goals should be considered when choosing therapy."⁷

Conclusion

CRPC has traditionally presented significant therapeutic challenges for clinicians and patients to uncover the best possible methods for halting disease progression and for improving survival and patient QOL. With the ongoing focus on new therapeutic targets and agents with novel mechanisms of action, the treatment of CRPC has been revolutionized over the past decade. These new and evolving agents have led to revised treatment algorithms for patient management, and are positioned to substantially alter the treatment environment for CRPC through improved individualization of therapy for patients with advanced and/or metastatic disease. Ongoing research will likely continue to bring additional novel agents and treatment methods to the forefront of care, and offer the potential to further reduce the spread of disease, improve survival, and ultimately enhance overall patient outcomes.

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