Progress in the Treatment of Advanced Prostate Cancer

Cora N. Sternberg, MD, Daniel P. Petrylak, MD, Ravi A. Madan, MD, and Chris Parker, MD

OVERVIEW

The androgen receptor (AR) is the most significant target for patients with metastatic castration-resistant prostate cancer (mCRPC). There is now irrefutable evidence that the AR axis is functional in most patients throughout the history of prostate cancer, is crucial from diagnosis to death, even in patients who have received hormonal manipulation, and represents a relevant therapeutic target in all phases of the disease. The potential mechanisms of tumor escape after castration are multifold, with each mechanism today representing a therapeutic opportunity. Phase III trials have been able to demonstrate improved overall survival (OS), improved quality of life, decreased skeletal-related events, and other important clinical benefits in young and elderly patients. After the initial positive results with docetaxel chemotherapy in improving OS, further research has resulted in five new treatments in the past few years. Immunotherapy with sipuleucel-T, cabazitaxel chemotherapy, the androgen biosynthesis inhibitor abiraterone acetate, the antiandrogen enzalutamide, and the radioisotope radium-223 have all been shown to improve OS in large-scale, well-conducted clinical trials. Proper understanding of mechanisms of resistance and of cross-resistance among these agents, sequencing, and combinations is now a priority.

Prostate cancer is the second most common cause of cancer worldwide.1 It is estimated that more than 29,000 men will die from metastatic prostate cancer in 2014.2 For patients who relapse after treatment of organ-confined disease or those who present with metastatic disease, testosterone suppression with hormone therapy is the foundation of therapy. Lowering testosterone and its precursors and altering the AR axis was the first method discovered that could control this disease.

The initial treatment for metastatic disease is androgen ablation, achieved either surgically or medically. Either modality should result in reduction in testosterone to levels less than 50 ng/dL, resulting in prostate tumor regression.3 Clinical response to androgen blockade is manifested by decline in serum prostate specific antigen (PSA), relief in pain from bone metastases, and improvement in neurologic symptoms from spinal cord compression when combined with high-dose steroids and radiation. Despite initial clinical and symptomatic improvement, nearly all men will progress to castration-resistant prostate cancer (CRPC). This state of disease is defined as progression of disease, either biochemically or objectively, despite castrate testosterone levels. The cutoff of testosterone less than 50 ng/dL has not been established for clinical utility, but rather for ease in clinical trial accrual. Before the advent of more effective chemotherapeutic, hormonal, immunotherapeutic, and radiological agents, CRPC historically had a dismal prognosis with median OS of 9 months to 12 months. Significant morbidity from disease progression in CRPC may be caused by anemia, urinary tract obstruction, spinal cord compression, pathologic fractures, pain, and cachexia.

Today, the AR still represents the most relevant target for patients with mCRPC. Although in the past prostate cancer has been referred to as “hormone refractory” or “androgen independent,” there is now irrefutable evidence that the AR axis is functional in most patients throughout the natural history of prostate cancer from diagnosis to death, and represents a therapeutic target that is relevant in all phases of the disease.

The potential mechanisms of tumor escape after castration with luteinizing hormone-releasing hormone (LHRH) analogs, female hormones, and LHRH antagonists are multifold, with each mechanism today representing a therapeutic opportunity. Phase III trials have been able to demonstrate improved survival, improved quality of life, decreased skeletal-related events, and other important clinical benefits in young and elderly patients.

mCRPC is a challenge; however, research has resulted in five new treatments in the past few years. Immunotherapy with sipuleucel-T, cabazitaxel chemotherapy, the androgen biosynthesis inhibitor abiraterone acetate, the antiandrogen enzalutamide, and the radioisotope radium-223 have all been shown to improve OS in large-scale, well-conducted clinical randomized phase III trials.4-11 Bone-targeted therapy has
also shown remarkable improvements in preventing skeletal-related events. Several agents have already been approved by the U.S. Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) and others are in advanced stages of development.

HORMONAL THERAPIES IN PROSTATE CANCER: THE NEW AND THE OLD
Advances in Targeting Androgen Receptor Signaling
The foundation of treatment for advanced prostate cancer is the suppression of gonadal androgens, which invariably leads to the development of castration-resistant disease. Until recently, there were few data evaluating hormone therapy in patients who had received multiple lines of hormone therapy and chemotherapy. In addition, there were no phase III randomized trials with the endpoint of improving OS in patients with asymptomatic or limited mildly symptomatic disease. The therapeutic arena has changed dramatically with the discovery and clinical development of novel agents that block testosterone synthesis and AR signaling (Table 1), and the success of both abiraterone acetate and enzalutamide in patients pre- and postdocetaxel.

Inhibitors of CYP17
There has been an increasing appreciation of the role of continuing androgen signaling mediated by adrenal, testicular, and intratumoral androgen synthesis. Among the molecular alterations in CRPC is the upregulation of androgen biosynthesis enzymes, leading to an increase in intratumoral androgen concentrations. Additionally, AR amplification and mutations in driving tumor growth have been comprehensively described. Cytochrome P450 enzyme 17 (CYP17) has an important role in the production of androgenic and estrogenic steroids. The antifungal ketoconazole was the first CYP17 inhibitor to be used in clinical practice for CRPC primarily before chemotherapy, but it has never been shown in a clinical trial to clearly improve survival and its side effects were often prohibitive.

Abiraterone Acetate
Abiraterone acetate (Zytiga, Janssen) is an oral inhibitor of CYP17 that is essential for androgen biosynthesis. Abiraterone inhibits 17 alpha-hydroxylase/C17,20 lyase (CYP17A1), an enzyme expressed in testicular, adrenal, and prostatic tumor tissues. CYP17 catalyzes two sequential reactions: (1) the conversion of pregnenolone and progesterone to their 17-alpha-hydroxy derivatives by its 17 alpha-hydroxylase activity, and (2) the subsequent formation of dehydropiandrosterone (DHEA) and androstenedione, respectively, by its C17,20 lyase activity. DHEA and androstenedione are androgens and precursors of testosterone. Inhibition of CYP17 activity by abiraterone decreases circulating levels of testosterone, the most essential ligand for the AR.

After oral administration of abiraterone acetate, the prod- rug form present in the commercial preparation is converted into the active form, abiraterone. This conversion is likely to be esterase-mediated and not CYP-mediated. The oral prod- rug is well absorbed and rapidly deacetylated in the liver. Administration with food increases absorption of the drug and, thus, has the potential to result in increased and variable exposures. Therefore, the drug should be consumed on an empty stomach. It is highly protein bound (>99%), and is metabolized in the liver by CYP3A4 and SULT2A1 to inactive metabolite and excreted by feces (approximately 88%) and urine (approximately 5%) with a terminal half-life of 12 ± 5 hours.

There were four phase I/II studies that showed impressive decreases in serum PSA of 50% or greater and contributed to the development of abiraterone both before chemotherapy, postchemotherapy and postketoconazole. Reductions in circulating tumor cells (CTCs) and radiological responses were also seen. Abiraterone leads to a rebound increase in luteinizing hormone (LH) and in adrenocorticotropic hormone (ACTH). Low-dose corticosteroids normalize mineralocorticoid levels, improve side effects, and have led to its development in combination with prednisone or prednisolone.

The pivotal phase III trial leading to approval of abiraterone was the COU-AA-301 randomized, double-blind, placebo-controlled trial of 1,195 patients with mCRPC who had failed one to two prior chemotherapy regimens (one with docetaxel) who were randomly assigned 2:1 to abiraterone acetate (1,000 mg) and prednisone (5 mg twice daily) or placebo and prednisone. The primary endpoint was OS and secondary endpoints included time to PSA progression, radiological progression free survival (rPFS) and PSA response. The majority of patients had radiographic evidence of disease progression before study entry.
At a median follow-up of 12.8 months, OS was longer in the abiraterone and prednisone arm than in the placebo and prednisone group (14.8 vs. 10.9 months; HR 0.65; 95% CI 0.54-0.77). The study was stopped by the Independent Data Monitoring Committee (IDMC) at the time of this interim analysis. All secondary endpoints were superior in the

<table>
<thead>
<tr>
<th>Agent</th>
<th>MOA</th>
<th>Studies</th>
<th>Trial Results</th>
</tr>
</thead>
</table>
| Abiraterone Acetate | Potent and selective inhibitor of CYP17-α-hydroxylase and C17,20-lyase | Phase III studies post- and pre-docetaxel with prednisone | COU-AA-301\(^{1,20}\) Met endpoint of OS  
OS: HR 0.74; 95% CI 0.638-0.859; p < 0.0001  
26% reduction in risk for death  
COU-AA-302\(^{18}\) met endpoint of rPFS and trend in OS  
OS: HR 0.79; 95% CI 0.66-0.95; p = 0.0151  
21% reduction in risk of death  
rPFS: HR 0.43 ; 95% CI 0.35-0.52 ; p < 0.0001  
57% reduction in rPFS  
Other combination trials ongoing |
| Enzalutamide        | AR antagonist, inhibits nuclear translocation and blocks DNA binding of the receptor and activation | Phase III studies post- and pre-docetaxel | AFFIRM\(^{9}\) met endpoint of OS  
OS: HR 0.631; 95% CI 0.529-0.752; p < 0.0001  
37% reduction in risk of death  
PREVAIL\(^{11}\) met endpoints of OS and rPFS  
OS: HR 0.706; 95% CI 0.60-0.84; p < 0.0001  
rPFS: HR 0.186; 95% CI 0.15-0.23; p < 0.0001  
MO CRPC PROSPER trial recruiting and other trials ongoing |
| Orteronel (TAK-700) | Selective, non-steroidal, small-molecule inhibitor of 17,20-lyase | Phase III studies post- and pre-docetaxel with prednisone | ELM-PCS did not meet primary endpoint of OS\(^{25}\)  
OS: HR 0.886; 95% CI 0.739-1.062; p = 0.1898  
Substantial regional differences in OS were seen  
rPFS: HR 0.78; 95% CI 0.653-0.885; p = 0.0038  
ELM-PC4  
Fully recruited-ongoing\(^{23}\)  
Others: orteronel vs. bicalutamide in mCRPC patients failing first-line LHRH agonists or surgical castration\(^{26}\)  
Orteronel vs. bicalutamide in hormone-naive prostate cancer patients failing on LHRH agonists\(^{29}\) |
| Galeterone (TOK-001) | AR antagonist and AR degrader and a CYP17 lyase inhibitor | Phase I/II ARMOR 1 and ARMOR 2 | ARMOR 2\(^{25}\)  
Reformulated galeterone  
Significant improvements in PSA response at 12 weeks in CRPC as compared with ARMOR1  
M1 treatment naive 2,550 mg QD PSA response: 90% \(=\) 30% and 81% \(\geq\) 50% |
| ARN-509             | AR antagonist, inhibits nuclear translocation and DNA binding of the receptor | Phase I/II | N = 30 with doses 30 mg to 480 mg  
PSA declines at 12 weeks \(\simeq\)50% in 46.7%\(^{45}\)  
Phase II trial recruited\(^{44}\)  
MO CRPC Spartan trial recruiting\(^{45}\) |
| ODM-201 ORM-1534I   | No CYP inhibition or induction with therapeutic doses | Phase I/II | ARCADES Trial\(^{46}\)  
Chemotherapy,  
CYP17-naive \(\simeq\)50% PSA: 65%  
Post-chemotherapy/CYP17-naive \(\simeq\)50% PSA 32%  
Post-CYP17 \(\simeq\)50% PSA: 9%  
MO CRPC trial planned |

Abbreviations: MOA, mode of action; OS, overall survival; HR, hazard ratio; CI, confidence interval; rPFS, radiographic progression-free survival; AR, androgen receptor; PSA, prostate specific antigen; CRPC, castration-resistant prostate cancer; LHRH, luteinizing-hormone releasing hormone; QD, every day.
abiraterone-treated patients; time to PSA progression (10.2 vs. 6.6 months; p < 0.001), PFS (5.6 vs. 3.6 months; p < 0.001) and PSA response rate (29% vs. 6%; p < 0.001). In all subgroups analyzed the abiraterone arm was favored although the confidence levels were less impressive in patients with a performance status of 2.

Abiraterone was well tolerated although mineralocorticoid-related adverse related events were slightly more frequent. Further analysis revealed that abiraterone had significant benefits compared with prednisone in terms of pain relief, patient-reported fatigue, delaying pain progression, and prevention of skeletal-related events. In an update of this study with 20.2 months follow-up, the median OS increased from 3.9 to 4.6 months and OS was longer in the abiraterone and prednisone group (15.8 vs. 11.2 months; HR 0.74; 95% CI 0.64-0.86; p < 0.0001).

Since abiraterone was effective after chemotherapy, the COU-AA-302 phase III trial was initiated. This randomized, double-blind, placebo-controlled trial recruited asymptomatic or mildly symptomatic chemotherapy-naive patients with mCRPC. Patients were randomly assigned 1:1 to abiraterone acetate (1,000 mg) and prednisone (5 mg twice daily) or placebo and prednisone. The coprimary endpoints were rPFS and OS. The study accrued rapidly and was stopped by the IDMC at the time of the first interim analysis.

The difference in rPFS was statistically significant with a HR of 0.43 (95% CI 0.35-0.52; p < 0.0001), representing a 57% reduction in the risk for progression and showed a trend toward improved OS, and significantly delayed clinical decline and initiation of chemotherapy by 26.5 months as compared with 16.8 months on placebo. At the third preplanned interim analysis, the median benefit was 5.2 months and there was a strong 56% trend in favor of abiraterone in terms of OS (HR 0.79; 95% CI 0.66-0.95; p = 0.0151), representing a 21% reduction in risk for death, once again not meeting the prespecified significance level by O'Brien-Fleming Boundary = 0.0035. These remarkable results have been practiced changing and many chemotherapy-naive patients with mCRPC are being treated earlier with abiraterone. In addition, abiraterone is being evaluated in different settings and in earlier-stage hormone-sensitive men beginning LHRH analogs or antagonists, as well as in combination with enzalutamide, chemotherapy, and radium-223.

**CYP17 Inhibitors in Development**

**Orteronel.** Other agents that target the AR signaling pathway through CYP17 are in clinical development. Orteronel (TAK 700) has a similar mechanism of action to abiraterone, a non-steroidal CYP17 inhibitor with potentially greater 17,20 lyase selectivity (i.e., for androgen as opposed to corticosteroid synthesis). Orteronel has been evaluated in two large placebo-controlled phase III trials (with prednisone in both arms) in men with progressive mCRPC, who are either chemotherapy-naive or postdocetaxel. The ELM-PC 5 trial postdocetaxel did not meet its primary endpoint of OS for the entire population. There were, however, significant improvements in time to PSA progression and PSA response after treatment with orteronel plus prednisone. Important regional differences during conduct of the study were influential because of the availability of abiraterone and other novel agents. Only 38% of patients in non-Europe/North America (NA) received subsequent therapy (including abiraterone 8%) compared with more than 50% of patients in either Europe or NA (including abiraterone 28% and 26%, respectively). In the non-Europe/NA population (36% of the overall population), orteronel plus prednisone was associated with improved OS (p = 0.019; HR 0.709).

Studies with this active agent have been completed or are enrolling patients in men with rising PSA and no evidence of metastatic disease (M0). As well as in combination with docetaxel. A randomized phase II study with the European Organisation for Research and Treatment of Cancer Genito-Urinary Cancers Group is comparing orteronel to bicalutamide in patients with mCRPC failing first-line treatment with LHRH agonists or surgical castration. The plan is to enroll 200 patients. The SWOG is also conducting a phase III trial of LHRH agonists plus bicalutamide compared with LHRH agonists plus orteronel for metastatic hormone-sensitive prostate cancer with an estimated enrollment of 1,486 patients.

**Galeterone**

Other agents are in earlier stages of development such as TOK-001 (galeterone, Tokai), which inhibits prostate cancer growth by multiple mechanisms. Preclinical studies have shown that galeterone selectively inhibits CYP17 lyase to prevent testosterone synthesis, antagonizes testosterone binding to the AR, and degrades the AR protein.

Galeterone was evaluated in four studies testing pharmacokinetics and formulation optimization in normal, healthy volunteers supporting development for all stages of prostate cancer and in a clinical proof-of-concept study in patients with CRPC. ARMOR1 was a phase I, open-label, dose-escalation trial of chemotherapy-naive patients with CRPC. However, the drug formulation used in ARMOR1 exhibited inconsistent gastrointestinal absorption because of a significant food effect. Galeterone was reformulated as a spray dried dispersion (SDD), which mitigated the food effect for the ARMOR2 study. ARMOR2 is a two-part phase II study designed to confirm the dose of the SDD formulation and demonstrate safety and efficacy in four distinct cohorts of patients with CRPC. Interim results of ARMOR2 have been presented. Significant improvements were seen in PSA response at 12 weeks as compared with M1-treated patients on the ARMOR1 study (Table 1).

**Androgen Receptor Antagonists**

Enzalutamide. Enzalutamide (Xtandi, Medivation and Astellas) is a novel AR antagonist that binds the AR with a higher affinity than bicalutamide, prevents nuclear translocation and DNA binding, induces apoptosis, and has no agonist activity when AR is overexpressed.

In a phase I/II trial of 140 patients with progressive metastatic CRPC, antitumor activity was noted at all doses, in-
cluding declines in serum PSA of 50% or more in 56 patients, responses in soft tissue in 22%, stabilization of bone disease in 56%, and conversion from unfavorable to favorable CTCs in 49%. This led to the phase III AFFIRM study of enzalutamide compared with placebo (prednisone was not required) in 1,199 patients with CRPC who had progressed after one to two prior chemotherapy regimens, including docetaxel chemotherapy. A planned interim analysis of the study after 520 events led the IDMC to unblind the study as it showed a 4.8-month improvement in median OS compared with placebo (18.4 vs. 13.6 months; HR 0.631; \( p < 0.0001 \)).27,28 A survival benefit was observed in all subgroups, although less benefit was seen in those with performance status of 2, similar to what was observed in the abiraterone trial. Confirmed PSA decline of more than 50% was seen in 54% as compared with 1.5% (\( p < 0.0001 \)) of placebo patients. Median time to PSA progression was 8.3 months as compared with 3 months (HR 0.248; \( p < 0.0001 \)). Side effects were minimal, with less than 1% seizures reported. Enzalutamide improved outcomes in both younger (< age 75) and elderly patients (\( \geq \) age 75), with comparable safety and tolerability.35

The PREVAIL study is a phase III randomized, double-blind, placebo-controlled trial in 1,717 chemotherapy-naive patients with metastatic CRPC.36 Asymptomatic or mildly symptomatic patients were randomly assigned 1:1 to oral enzalutamide or placebo. The study met its coprimary endpoints of OS and rPFS. At interim analysis, the IDMC recommended the study be stopped early and enzalutamide offered to study participants. They observed a 29% reduction in the risk for death (HR 0.706; 95% CI 0.60-0.84; \( p < 0.0001 \)) and an 81% reduction in the risk for rPFS or death (HR 0.186; 95% CI 0.15-0.23; \( p < 0.0001 \)).11

The phase II TERRAIN trial comparing enzalutamide with bicalutamide has enrolled patients who progressed while on LHRH analog therapy or after surgical castration.37 PFS is the primary endpoint. Results of a phase II trial evaluating enzalutamide monotherapy in hormone-naive patients38 were reported during the 2013 ECC meeting.39 Other studies are evaluating the combination of enzalutamide and abiraterone (Alliance trial) or treatment beyond progression with enzalutamide (PLATO trial).40 A large phase III trial in patients with M0 CRPC called PROSPER trial is also recruiting.41

**ARN-509**

ARN-509, a novel antiandrogen, has a similar mechanism of activity to enzalutamide42 and has undergone early evaluation in 30 patients with progressive CRPC who received continuous daily oral ARN-509 at doses between 30 mg and 480 mg; a maximum efficacious dose of 240 mg daily was selected for phase II.43 A phase II trial will enroll approximately 127 patients in three cohorts; M0 CRPC, M1 abiraterone-naive, and M1 abiraterone-pretreated patients.44 This agent should cross the blood-brain barrier less than enzalutamide and is now being studied in the SPARTAN trial for patients with M0 CRPC in a multicenter, randomized, phase III study with metastases-free survival as the primary endpoint.45

**ODM-201**

ODM-201 is a new generation AR antagonist that is structurally dissimilar from enzalutamide and ARN-509. It inhibits AR function by blocking nuclear translocation and does not enter the brain in nonclinical models, unlike other antiandrogens. ODM-201 has no agonist activity when the AR is overexpressed and has extremely high affinity for the AR. It has no CYP inhibition or induction with therapeutic doses. In the phase I/II ARADES trial PSA response at 12 weeks was evaluated at doses of 200 mg, 400 mg and 1,400 mg. At the 1,400 mg dose: six out of seven patients (86%) had a 50% or greater decrease in PSA. The greatest activity was seen in patients who were chemotherapy- and CYP17I-naïve, although responses were also seen postchemotherapy and CYP17I.46

An open, phase I trial assessed the bioavailability, and the effect of food on the bioavailability of ODM-201 600 mg tablets compared with a 600 mg capsule formulation. ODM-201 600 mg twice daily as tablets has comparable pharmacokinetics to capsules used in the phase II ARADES trial.47,48 A trial is planned in patients with M0 CRPC.

**Resistance to AR-Directed Therapy**

Resistance to AR-directed therapy is too complex a topic to address in great detail in this article (Sidebar 1). Androgen production by adrenal glands and prostate tumor cells may explain abiraterone’s effects. However, studies are elucidating various mechanisms of resistance to abiraterone that may be mediated by amplification of CYP17 (indicating a potential role for dose escalation of abiraterone).49 Other competing molecular mechanisms may also come into play to induce resistance despite evidence that the AR in CRPC is continuing to provide the growth and survival signals for tumors.50,51

There is increasing and emerging evidence of cross-resistance among abiraterone, enzalutamide, and taxanes that also affect AR ligand dependent and independent binding and inhibit AR nuclear translocation.52

As many as 80% of CRPCs have been reported to carry an elevated AR gene copy number, and approximately 30% have a high-level amplification of the gene. AR mutations are also commonly observed and have been found in approximately 10% to 30% of patients with CRPC. Point mutations of the AR may maintain (promiscuous) ligand-binding domain-dependent activation. Mutations in the AR such as AR F876L may confer resistance to enzalutamide and convert enzalutamide into an AR agonist.53

The frequency and significance of AR splice variants is also still unclear. These aberrations most likely are selected for during therapy. Interestingly, these aberrations lead to activation of the receptor, despite treatment-induced emergence of therapy-resistant tumor clones. Therefore, future novel treatment strategies should focus on suppressing AR activity in CRPC. Signaling cross-talk with the PI3K/AKT/ERK/mTOR family may play an important role as well as upregulation of AR cofactors.50,54

The glucocorticoid receptor may be another important mechanism of resistance and provide another mechanism of escape from AR blockade through expansion of cells primed...
to drive AR target genes via an alternative nuclear receptor on drug exposure.55

**REVISITING THE ROLE OF CHEMOTHERAPY IN PROSTATE CANCER**

Historically, chemotherapy for advanced prostate cancer was viewed as toxic and ineffective, without a significant effect on survival. Two reviews of single-agent cytotoxic therapy in men with CRPC demonstrated that objective responses to chemotherapy were 6.5% to 8.7%, without improvement in survival.56,57 Thus, chemotherapy was generally limited to palliation for those patients who had symptomatic bone pain. Mitoxantrone and prednisone was approved by the FDA based on palliation of bone pain.58-60 An improvement by a decrease in two points on a six-point pain scale was observed to be superior in men treated with mitoxantrone 12 mg/m² every 3 weeks (29%) compared with prednisone 10 mg orally once daily alone (12%). A CALGB trial of mitoxantrone/hydrocortisone compared with hydrocortisone demonstrated no difference in OS. Thus, until 2004, CRPC was considered a chemotherapy-resistant disease with no randomized study demonstrating a survival with chemotherapy.

**Docetaxel for CRPC**

Derived from the needles of *Taxus baccata*, docetaxel reversibly stabilizes microtubules and prevents their depolymerization.61 Apoptosis of cancer cells result as a consequence of microtubule aggregation, as well as through phosphorylation of an oncoprotein, Bcl-2.62 Both in vitro and in vivo studies found docetaxel to be effective against human prostate cancer cell lines DU 145, PC-3, and LNCaP.63,64 Phase I and II trials of docetaxel administered as a single agent or in combination with estramustine phosphate demonstrated PSA decline rates of greater than 50% in 36% to 69% of treated patients, objective response rates of 17% to 38%, and median survivals of 20 to 23 months.65-68 Two phase III trials compared docetaxel-based combination regimens with standard mitoxantrone/prednisone in men with progressive CRPC (Fig. 1, Table 2).

Two different dosing schedules of docetaxel/prednisone were compared with mitoxantrone/prednisone in the TAX 327 trial in men with mCRPC.69 Patients were permitted to have prior estramustine but other prior cytotoxic regimens were not permitted; 1,006 patients were randomly assigned to one of three arms: (1) docetaxel 75 mg/m² every 3 weeks, (2) docetaxel 30 mg/m² weekly for 5 of 6 weeks, or (3) mitoxantrone 12 mg/m² every 3 weeks. Prednisone at 5 mg orally twice daily was given to all patients.

The median OS was superior to mitoxantrone only in the every 3 week docetaxel arm (18.9 vs. 16.4 months; p < 0.009). Weekly docetaxel did not result in a statistically significant OS advantage (17.4 vs. 16.4 months; p = 0.36). Compared with mitoxantrone/prednisone, the reduction in the risk for death was 24% and 9% for the every 3 week and weekly docetaxel arms, respectively. An updated survival analysis found that more patients survived 3 years when treated with docetaxel either every 3 weeks or weekly (18.6% and 16.6% vs. mitoxantrone 13.5%).70 PSA declines of more than 50%
were significantly higher (45% and 48%) in the 3-week and weekly docetaxel groups, respectively, than in the patients treated with mitoxantrone (32%). No significant differences in objective response rates were observed in the three treatment arms. Docetaxel therapy was associated with superior palliation of bone pain; 33% and 31% in the every 3 weeks and weekly regimens as compared with 21% in the mitoxantrone group. Quality of life, when using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) instrument was significantly better in the docetaxel groups as compared with the mitoxantrone group.

Neutropenia was more frequent in the every 3 week docetaxel group (32% vs. 21.7% in the mitoxantrone group). Grade 3 and 4 neutropenia occurred in 3% of patients in the docetaxel every 3 week group, with 2.7% experiencing febrile neutropenia. Neuropathy and alopecia were also more frequent in the docetaxel arms; however, the patterns of toxicity were not significantly different between the docetaxel and mitoxantrone groups.

SWOG led an intergroup study comparing docetaxel/estramustine with mitoxantrone/prednisone.71 Men randomly assigned to the experimental arm received estramustine at 280 mg orally three times daily on days 1 through 5, docetaxel at 60 mg/m² intravenously on day 2 every 21 days, and dexamethasone 60 mg orally in three divided doses before docetaxel. In contrast to TAX 327, patients did not receive methasone 60 mg orally in three divided doses before docetaxel. In contrast to TAX 327, patients did not receive prednisone. Mitoxantrone was administered at the same dosage and schedule as in TAX 327 study. Dose escalation to docetaxel 70 mg/m² or mitoxantrone 14 mg/m² was permitted for those patients who did not experience grade 3 or 4 toxicity in the first cycle of therapy. Docetaxel combined with estramustine improved median OS (17.5 vs. 15.6 months; p = 0.01) and progression-free survival (6.3 vs. 3.2 months; p < 0.001). A greater percentage of patients demonstrated a more than 50% PSA decline (50% vs. 27%; p < 0.0001) with docetaxel/estramustine than mitoxantrone/prednisone. A trend toward an improved rate of objective responses in measurable soft-tissue disease was noted in favor of every 3 week docetaxel (17% vs. 11%; p = 0.030). Palliation of bone pain was not found to be statistically different in the two arms. Overall, the relative risk for death was reduced by 20% with docetaxel and estramustine as compared with mitoxantrone and prednisone (HR for death 0.80; 95% CI 0.67-0.97).

Grade 3 and 4 toxicities were higher in the docetaxel/prednisone arm compared with mitoxantrone/prednisone. The incidence of grade 3 or 4 cardiovascular (15% vs. 7%; p = 0.001), neurological (7% vs. 2%; p = 0.001), neutropenic fever (5% vs. 2%; p < 0.001), gastrointestinal (20% vs. 5%, p < 0.001) and metabolic disturbances (6% vs. 1%, p < 0.001) were increased in the experimental arm. However, there was not a higher rate of discontinuation from the study and there was no increase in toxic deaths in the docetaxel/estramustine arm. Prophylactic anticoagulation with coumadin and aspirin was added to the experimental arm halfway through the trial. A post hoc analysis of toxicity revealed that anticoagulation decreased the rate of cardiac ischemia but not the rate of thrombosis. Evaluation of the use of anticoagulation is limited, as the trial was not designed to detect a difference in vascular events.

**Docetaxel-Based Investigational Therapies**

A number of novel agents have been investigated in combination with docetaxel in an attempt to improve OS. The results with many trials of docetaxel-based combination therapy have been disappointing. Although serum VEGF levels correlate inversely with survival, antiangiogenesis agents (bevacizumab, aflibercept, lenalidomide) combined with docetaxel/prednisone have not improved OS. Combinations of bone targeted agents such as atrasentan, dasatinib, and ZD4054 with docetaxel have also had disappointing results. Vitamin D (calcitriol, DN-101 combined with weekly docetaxel demonstrated no OS advantage compared with docetaxel/prednisone. Potential reasons for the failure of combination therapy include marginal activity of the agents that were combined with docetaxel, as well as dose reductions of docetaxel due to overlapping toxicities.

**Cabazitaxel**

Granted fast track designation in November 2009, cabazitaxel (Jevtana, Sanofi) combined with prednisone was approved by the FDA in June 2010 and by EMA in March 2011 for the treatment of men who had previously received a docetaxel-based regimen for CRPC. Cabazitaxel is the third cytotoxic agent to be approved by the FDA for castration-resistant disease, and the second to demonstrate a survival benefit compared with mitoxantrone combined with prednisone.

---

**TABLE 2. Docetaxel-Based Phase III Trials**

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Regimen</th>
<th>Objective Measurable Response Rate (%)</th>
<th>PSA Response Rate (%)</th>
<th>% with Palliative Response</th>
<th>Time to Progression (Months)</th>
<th>Survival (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG 9916</td>
<td>Docetaxel/estramustine</td>
<td>17</td>
<td>50</td>
<td>17*</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Mitoxantrone/prednisone</td>
<td>10</td>
<td>27</td>
<td>11</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>TAX 327</td>
<td>Docetaxel (Every 3 weeks)/prednisone</td>
<td>12*</td>
<td>45</td>
<td>35</td>
<td>7.9*</td>
<td>18.9</td>
</tr>
<tr>
<td></td>
<td>Docetaxel (every week)/prednisone</td>
<td>8*</td>
<td>48</td>
<td>31</td>
<td>8.2*</td>
<td>17.4</td>
</tr>
<tr>
<td></td>
<td>Mitoxantrone/prednisone</td>
<td>7*</td>
<td>32</td>
<td>22</td>
<td>7.8*</td>
<td>16.5</td>
</tr>
</tbody>
</table>

*Did not reach statistical significance.
Mechanism of Action

Similar in structure and antitumor mechanism to paclitaxel and docetaxel, cabazitaxel is a novel second-generation, semisynthetic taxane that induces cell death by microtubule stabilization through inhibition of disassembly. Cabazitaxel binds the N-terminal amino acids of the beta-tubulin subunit, and promotes stabilization of microtubules and the mitotic spindle. In addition to activity against paclitaxel- and docetaxel-sensitive human cervical, breast, leukemia, and prostate cancer cell lines, cabazitaxel demonstrates activity in taxane-resistant cell lines. The explanation for this pattern of activity stems from cabazitaxel’s effect on the efflux pump of P-glycoprotein, responsible for the multidrug resistance phenotype. Expressed in a variety of human tumors including prostate cancer, P-glycoprotein is responsible for the adenosine-5'-triphosphate (ATP) dependent extrusion of natural product chemotherapeutic agents such as doxorubicin, vinca alkaloids, as well as paclitaxel and docetaxel. The extra methyl groups found on cabazitaxel are more effective in ATP-dependent efflux pump of P-glycoprotein than similarly placed hydroxyl groups on docetaxel and paclitaxel. This phenomenon may also be responsible for the increase in central nervous system accumulation of cabazitaxel with increasing plasma concentrations, demonstrated in rodent models; P-glycoprotein is known to be expressed in the capillary endothelium of the brain and may be responsible for crossing the blood-brain barrier.

Phase III Studies of Cabazitaxel in Docetaxel Pretreated Patients with CRPC

The activity of cabazitaxel demonstrated against taxane-resistant cell lines, as well as the responses observed in phase I, led investigators to study cabazitaxel in men with CRPC previously treated with docetaxel. The TROPIC trial randomized 755 men to cabazitaxel 25 mg/m² every 3 weeks or mitoxantrone. Of the 18 patients on the cabazitaxel arm, 4 (22%) had a prior history of radiation therapy. A higher rate of neutropenia was observed in patients aged older than 75 years. Diarrhea also was observed at an 8.6% higher rate in patients who had a prior history of radiation therapy. A higher rate of death from adverse events was noted in patients treated on the cabazitaxel/prednisone arm when compared with mitoxantrone/prednisone. Of the 18 patients on the cabazitaxel arm who died of adverse events, seven patients died of neutropenic sepsis, in contrast to one patient on the mitoxantrone arm. Prophylactic colony stimulating factors were not administered during the first cycle of therapy, which could possibly reduce the risk for neutropenic death. This pattern of toxicity has lead the FDA to recommend administration of prophylactic growth factors in patients treated with cabazitaxel who are aged older than 65 years, have had extensive prior radiation, poor nutrition, previous febrile neutropenia, poor performance status, or other serious comorbidities. In a report of a global early access program performed in Italy, patients with CRPC treated with six cycles of cabazitaxel experienced neutropenia (33.9%), leukopenia (15.6%), anemia (6%), and asthenia. Given cabazitaxel’s efficacy in patients pretreated with docetaxel, it would be logical to evaluate cabazitaxel as frontline chemotherapy in men with CRPC. An international randomized trial of docetaxel combined with prednisone compared with cabazitaxel (20 mg/m² or 25 mg/m²)/prednisone is underway. To further define the optimal dose, a second study is randomizing patients to 20 mg/m² or 25 mg/m² of cabazitaxel. TAXYNERGY is a randomized phase II study of first-line docetaxel compared with first-line cabazitaxel, with a potential switch to the alternative taxane if patients do not achieve a more than 30% PSA decline after four cycles of therapy. Studies are also underway evaluating cabazitaxel combined with a novel antisense agent that targets clusterin, an antiapoptotic agent, compared with cabazitaxel alone.

Sequencing of Treatments

The approvals of abiraterone, sipuleucel-T, and potential approval of enzalutamide in the predocetaxel space have resulted in the use of chemotherapy later in the
course of CRPC. Although both asymptomatic and symptomatic patients were entered in both SWOG 99-16 and TAX 327, the relatively lower toxicity of these four agents has led to their preferential use over docetaxel. It is unclear whether administration of any of these agents before either docetaxel or cabazitaxel reduces efficacy or increases toxicity of these cytotoxic agents. Retrospective studies have been performed in small, select groups of patients and are difficult to apply to individual treatment decisions. There are theoretical reasons why response patterns may be sequence dependent. Docetaxel is known to inhibit the translocation of the AR from the cytoplasm into the nucleus, and, thus, can be cross resistant with either abiraterone or enzalutamide.85,86 Pond et al found that patients previously treated with ketoconazole/hydrocortisone in a randomized trial of docetaxel with or without AT-101, a novel Bcl-2 inhibitor, had numerically and consistently worse outcomes than patients not exposed to prior ketoconazole; although, the estimated differences did not attain statistical significance.87 A 6.5-month shorter median survival was reported in a retrospective evaluation of 35 patients who received docetaxel after abiraterone treatment. Patients who did not initially respond to abiraterone were also found to be resistant to docetaxel. In a small subgroup of patients treated with cabazitaxel after abiraterone alone, abiraterone followed by enzalutamide, or in enzalutamide alone, 16/41 of patients (39%) demonstrated a more than 50% PSA decline, with a median survival of 15.8 months.88 Clearly, why response patterns may be sequence dependent. Docetaxel does not require leukapheresis. Genetically modified viruses strategy is logistically more feasible than sipuleucel-T since it appears to have a greater opportunity for success.

Both docetaxel and cabazitaxel have antitumor activity in chemotherapy-naive and chemotherapy-pretreated patients, respectively. Combination therapy with docetaxel has not resulted in increased survival. Although randomized trials are currently underway to define which of these two agents should be administered as front-line therapy, the optional sequences of these agents with newer agents such as abiraterone, enzalutamide, and radium-223 have yet to be defined.

INTEGRATING IMMUNOTHERAPIES IN PROSTATE CANCER TREATMENT

Perhaps one of the more surprising developments in the last 50 years of prostate cancer research is the emergence of immunotherapy as a viable treatment option. Rarely considered in the same category as classic immunologic tumors such as melanoma or renal cell carcinoma, there may be several reasons why immunotherapy can be effective in prostate cancer including the presence of distinct tumor antigens, an indolent disease course, and emerging data suggesting that antiandrogens can enhance immune responses.89 Table 3 describes selected ongoing trials in prostate cancer evaluating immunotherapy.

Sipuleucel-T demonstrated an OS benefit in randomized phase III trials leading to its FDA approval in 2010 for minimally symptomatic mCRPC.4,70 This therapeutic cancer vaccine is generated from a patient’s own peripheral immune cells procured via leukopheresis. The cells are then processed over 48 hours at a centralized facility where they are exposed to a fusion peptide of granulocyte macrophage colony-stimulating factor (sering as immune adjuvant) and pulmonary alveolar proteinosis. The ultimate goal of this procedure is to activate the immune cells ex vivo and then reinfuse them into the patient with the long-term objective of a sustained antitumor immune response.

Two other immune-based therapies are in the late stages of clinical testing. Ipilimumab, the immune checkpoint inhibitor approved for the treatment of metastatic melanoma, is currently being evaluated in mCRPC. A preliminary clinical trial suggested that ipilimumab with radiation to metastatic lesions, as a means to enhance immune response, was safe and associated with some PSA responses.91 Although a phase III study in patients previously treated with chemotherapy evaluated ipilimumab (with a single dose of radiation) did not meet its primary endpoint of improved OS, the results were promising.92 There was an interesting trend of improved OS in patients treated with ipilimumab and radiation compared with radiation and placebo (11.2 vs. 10 months; HR 0.85; p = 0.053) and a secondary analysis suggested that patients with lower tumor burden performed better. Based on these data, the phase III trial in chemotherapy-naive patients,93 who are treated at an earlier stage of mCRPC would appear to have a greater opportunity for success.

A second agent currently in phase III testing in chemotherapy-naive, minimally symptomatic mCRPC is Prostvac (Bavarian Nordic).94,95 This pox viral-based vaccine strategy is logistically more feasible than sipuleucel-T since it does not require leukopheresis. Genetically modified viruses

### TABLE 3. Selected Ongoing Trials in Prostate Cancer Evaluating Immunotherapy

<table>
<thead>
<tr>
<th>ClinicalTrials.gov Identifier</th>
<th>Treatment Arms</th>
<th>Phase</th>
<th>Patient Population</th>
<th>Primary End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01057810</td>
<td>Ipilimumab versus placebo</td>
<td>Phase III (completed accrual)</td>
<td>Chemotherapy-naive mCRPC</td>
<td>Overall Survival</td>
</tr>
<tr>
<td>NCT01322490</td>
<td>Prostvac + GM-CSF versus Prostvac alone versus placebo</td>
<td>Phase III</td>
<td>Chemotherapy-naive mCRPC</td>
<td>Overall Survival</td>
</tr>
<tr>
<td>NCT01867333</td>
<td>Prostvac + enzalutamide versus enzalutamide</td>
<td>Phase II</td>
<td>Chemotherapy-naive mCRPC</td>
<td>Time To Progression</td>
</tr>
<tr>
<td>NCT01981122</td>
<td>sipuleucel-T with enzalutamide versus sipuleucel-T followed by enzalutamide</td>
<td>Phase II</td>
<td>mCRPC</td>
<td>Immune Response at 1 year</td>
</tr>
</tbody>
</table>

Abbreviations: mCRPC, metastatic castration-resistant prostate cancer; GM-CSF, granulocyte macrophage colony-stimulating factor.
serve as a vehicle to enhance antigen presentation of PSA in vivo. Phase II studies suggested the ability to improve OS and enhance PSA-specific T cells. With the phase III results of these two agents expected in the coming years, the immunotherapy options for prostate cancer could be significantly increased.

One complicating aspect of modern immunotherapy for clinicians is that these treatments do not appear to slow disease progression in the short term. Although this is often an object of concern raised for sipuleucel-T, it has also been seen with Prostvac (phase II, prostate cancer) and ipilimumab (phase III metastatic melanoma) when used as monotherapy. In this context, these findings are suggestive of a class effect and perhaps, with this understanding, the utility of such therapies could be better understood. One hypothesis suggests that these immunotherapies exert their effect on tumors by slowing growth rate over time, thereby suggesting in the short term that the cancer is “progressing” although during the long-term the slowed growth rate can enhance survival. This hypothesis takes into account that immunotherapy is very different from standard therapeutics in that if there is successful immune activation the ensuing antitumor effect will be sustained beyond the period of treatment administration. Thus, even after patients complete their course of immunotherapy, immune response may continue over time, slow tumor growth, and potentially lead to improved OS. Several trials are underway to prospectively evaluate this hypothesis including the phase III Prostvac trial. If accurate, this not only explains the apparent lack of short-term benefit but also highlights the need to treat patients earlier in the disease process to maximize the clinical effect (Fig. 2).

If immunotherapy can exert its benefits over prolonged time periods, then starting earlier in the disease process may yield even greater clinical effect. Vaccines (sipuleucel-T and Prostvac) may be the best candidates for this since they have negligible side effect profiles allowing for the potential to start treatment in asymptomatic patients with nonmetastatic or even in the (neo)adjuvant setting. The latter prospect is especially attractive, given that radiation has been shown to enhance antigen presentation by tumor cells making them more recognizable to the immune system and, thus, potentiating a greater antitumor effect. Furthermore, androgen deprivation therapy (ADT) has been shown to enhance thymic production of T cells that, if activated by immunotherapy, could be directed toward prostate cancer cells. Similar findings have also been seen with enzalutamide in preclinical studies. Furthermore, data suggest that ADT can reduce immune tolerance of prostate cancer antigens while also increasing T cell trafficking to the prostate. Of additional note, docetaxel has also been shown to enhance immunologic killing in combination with vaccines in preclinical models. These findings have important implications for the development of new treatment strategies. Early immunotherapy combinations with ADT (with or without enzalut-

---

**FIG 2. Hypothesis: Immunotherapy may alter tumor growth rates, thereby improving survival but not short-term disease progression.**

Retrospective data suggest that immunotherapy when used as a single agent may alter the growth rate of tumors over time. In this figure, the dashed line indicates the unaltered growth rate of tumor resulting in mortality of the patient at point #1. If immunotherapy (A and B) can slow the growth rate in the tumor (C) then perhaps such a treatment can prolong survival (#2 and #3). Immunotherapy administered earlier (A) would potentially have a greater effect on survival (#3) than immunotherapy administered later (B, #2). Regardless, in the short term there would be an appearance of disease progression (D). Although these findings represent what could happen when immunotherapy is used alone, the effect on survival could be enhanced when used in combination with other therapies. Current clinical trials are evaluating this hypothesis.
THE EVOLUTION OF RADIOPHARMACEUTICALS IN PROSTATE CANCER

A role for radiopharmaceuticals in prostate cancer was first tested 50 years ago. Phosphorus-32 was given intravenously to men with painful bone metastases. Phosphorus is a normal constituent of bone, and phosphorus-32 decays with the emission of beta particles. It was therefore argued that phosphorus-32 would localize to sites of bone synthesis, including metastatic sites, and deliver local radiotherapy. Early case reports observed a palliative effect with resolution of bone pain.107

Since then, several bone-seeking, beta-emitting radiopharmaceuticals have been approved for the treatment of prostate cancer, including strontium-89 and samarium-153-ethylendiaminetetramethylene phosphonic acid (EDTMP). Strontium-89 localizes to bone by virtue of its chemical similarity to calcium, whereas samarium-153-EDTMP achieves bone-targeting because of the bisphosphonate moiety.

The clinical utility of strontium-89 was established by two pivotal randomized controlled trials in the 1990s. The Canadian trial randomly assigned 126 men with bone pain from CRPC, all of whom received external beam radiotherapy, to 400 MBq strontium-89 or placebo.108 The men allocated to strontium-89 showed significant benefits in terms of need for analgesia, new sites of pain, freedom from further external beam radiotherapy, and physical activity. The British trial randomly assigned 284 patients with CRPC and painful bone metastases to receive external beam radiotherapy or 200 MBq of strontium-89.109 Pain relief at the index site was equivalent, but fewer patients reported new site of pain after strontium-89 than after external beam radiotherapy (36% vs. 58%; p < 0.05), and fewer required additional external beam radiotherapy within 12 weeks (3% versus 25%, p < 0.01). The role of samarium-153 has been studied in three randomized controlled trials that included men with CRPC.110-112 These trials demonstrated effective pain relief for samarium-153 in comparison with placebo.

Although approved for the treatment of CRPC, strontium-89 and samarium-153-EDTMP have not been widely used. To a large extent, this reflects concern about their hematologic toxicity. Anemia, leucopenia, and thrombocytopenia are common, occurring in as many as 80% of patients. Furthermore, the myelosuppression can be relatively prolonged, with the platelet nadir at around 6 weeks after strontium-89. It has been standard practice to use strontium-89 or samarium-153 after, rather than before, cytotoxic chemotherapy, given the concern that prior radiopharmaceutical treatment could impair bone marrow reserve.

About 10 years ago, Roy Larsen, a Norwegian radiobiologist, postulated that a bone-seeking alpha-emitter should be both more effective and less toxic than the beta-emitters. Alpha particles are approximately 7,000 times heavier than beta particles, and as few as one or two hits can be sufficient for cell death, in comparison with hundreds or even thousands of hits required from beta particles. In addition, alpha particles have a very short path length (<100 μm) that might, therefore, spare surrounding healthy bone marrow, thereby limiting hematologic toxicity. Larsen identified radium-223 as a suitable bone-targeted alpha-emitter for clinical testing.113

Subsequently, a series of phase I and phase II trials demonstrated the safety of radium-223, together with activity in terms of serum markers of bone turnover and PSA changes, and also raised the possibility that treatment with radium-223 would improve overall survival.114-117 These data led to the phase III ALSYMPCA trial that was reported in 2013,10 as a result of which radium-223 has now been approved for use in symptomatic mCRPC.

ALSYMPCA was an international, randomized, double-blind, placebo-controlled, phase III study comparing best standard care plus radium-223 with best standard care plus placebo in men with mCRPC. Eligibility was restricted to men with symptomatic bone metastases in the absence of known visceral disease. Radium-223 was given at a dose of 50 kBq/kg, every 4 weeks for six cycles. The primary endpoint was OS, which was improved by radium-223 with a HR of 0.7 (95% CI 0.58-0.83; p < 0.001), which translated to a median survival benefit of 3.6 months. All the other secondary efficacy endpoints were also met, with a 6-month delay in median time to first symptomatic skeletal event (HR 0.66; 95% CI 0.52 to 0.83; p < 0.001), and a significant improvement in quality of life measured using FACT-P. The incidence of adverse events and serious adverse events was lower in the radium-223 group than in the placebo group. Hematologic toxicity was unusual. For example, grade 3/4 thrombocytopenia was seen in 6% for radium-223 compared with 2% for placebo.

These data may underestimate the true benefit of radium-223 on survival. The trial was blinded so patients did not know whether they were getting radium-223 or placebo, and only around two-thirds of men completed all six cycles of radium-223. Some patients likely stopped study drug because they were uncomfortable with their PSA rising and the possibility they were receiving an inactive therapy. In routine clinical practice, compliance with radium-223 should be better, now that it is known to be safe and effective and with only a modest PSA response rate. Furthermore, the current schedule of six cycles of radium-223 at a dose of 50 kBq/kg every 4 weeks may not be the optimal schedule. Future trials will ex-
explore the use of higher doses and increasing the number of cycles.

For the past 50 years, we have known that bone-seeking beta-emitters offered palliative benefits to men with mCRPC at the cost of significant hematologic toxicity. They have been little used. Radium-223 is the first bone-seeking alpha-emitter, and it offers not just symptom palliation but also improved OS, prevention of skeletal events, and improved quality of life, together with a favorable safety profile. It seems clear that radiopharmaceuticals are set to play a much more important role in the management of CRPC in the years to come.

Disclosures of Potential Conflicts of Interest

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked “L” indicate leadership positions. Relationships marked “T” are those held by an immediate family member; those marked “B” are held by the author and an immediate family member. Relationships marked “U” are uncompensated.

Employment or Leadership Position: None. Consultant or Advisory Role: Chris Parker, Bayer Schering Pharma; BNIT. Daniel P. Petrylak, Astellas Pharma; Bellicum Pharmaceuticals; Bristol Myers Squibb; Dendreon; Egenix; Ferring; Genetech; Johnson & Johnson; Millennium; Progencis. Stock Ownership: None. Honoraria: Chris Parker, Astellas Pharma; Bayer Schering Pharma; Janssen-Cilag; Sanofi; Takeda. Cora N. Sternberg, Astellas Pharma; Bayer; Ipsen; Johnson & Johnson. Research Funding: Daniel P. Petrylak, Bayer; Boehringier Ingelheim; Celgene; Dendreon; Johnson & Johnson; Medivation; Progencis; Sanofi. Cora N. Sternberg, Cougar Biotechnology. Expert Testimony: None. Other Remuneration: None.

References

21. Rathkopf DE, Smith MR, de Bono JS, et al. Updated interim analysis (IA) of COU-AA-302, a randomized phase III study of abiraterone acetate (AA) in patients (pts) with metastatic castration-resistant pros-
tate cancer (mCRPC) without prior chemotherapy. J Clin Oncol. 2013;31:6s (suppl; abstr 5).


