Recent Developments in Treatments for Metastatic Castration-resistant Prostate Cancer—A Mechanistic Perspective

Guru Sonpavde, MD[1] and E David Crawford, MD[2]

1. Oncologist, Comprehensive Cancer Center, Department of Medicine, Section of Medical Oncology, University of Alabama at Birmingham, Birmingham, Alabama, US; 2. Professor of Surgery/Urology/Radiation Oncology, Head of Urologic Oncology, E David Crawford Endowed Chair in Urologic Oncology, University of Colorado, Denver, Colorado, US

Abstract

Over the past decade, the treatment landscape in metastatic castration-resistant prostate cancer (CRPC) has markedly changed, with the introduction of three new chemotherapeutic agents. The mechanism of CRPC is not fully understood, but it may result from multiple pathways, including a loss or androgen receptor (AR) specificity and increased downstream signalling activity that provide multiple targets for therapeutic agents. For some years, docetaxel was the mainstay of treatment in CRPC, but recently, cabazitaxel (a microtubule inhibitor), sipuleucel-T (a cancer vaccine), and abiraterone acetate (a CYP17 inhibitor) were approved for CRPC treatment. In Phase III clinical trials, these agents have shown significant improvements in survival—over mitoxantrone (for cabazitaxel) and over placebo (for sipuleucel-T and abiraterone acetate)—and were well tolerated. There are also two treatments in late-stage development, MDV3100 (an oral AR antagonist) and radium-223 (an isotope that creates breaks in double-stranded DNA). These have also shown improvements in survival in Phase III trials; their regulatory approval is expected soon. The modes of actions of the existing and new drugs in CRPC are varied, but some are complementary and investigations of different combinations of these medications are much needed; they may enhance efficacy, further extend survival, and improve outcomes in this formerly untreatable disease.

Keywords

Metastatic castration-resistant prostate cancer, androgen pathway, mechanism of disease, chemotherapy, combination treatments

Disclosure: Guru Sonpavde, MD, has been on the speakers bureau for Sanofi-Aventis, Janssen, and Amgen and on advisory boards for Astellas; he has received research support from Celgene, Pfizer, BMS, and Bellicum. E David Crawford, MD, has been on advisory boards for Ferring, Janssen, Dendreon, Medvation, and Astellas.
Acknowledgment: Editorial assistance was provided by Angela Chan, Medical Writer at Touch Briefings, and was funded by Janssen.
Received: August 8, 2012 **Accepted:** September 11, 2012 **Citation:** *Oncology & Hematology Review*, 2012;8(2):89–93 *DOI: 10.17925/OHR.2012.08.2.89*
Correspondence: E David Crawford, MD, University of Colorado, Denver, Mail Stop # F 710, PO Box # 6510, Aurora, CO 80045, US. E: david.crawford@ucdenver.edu

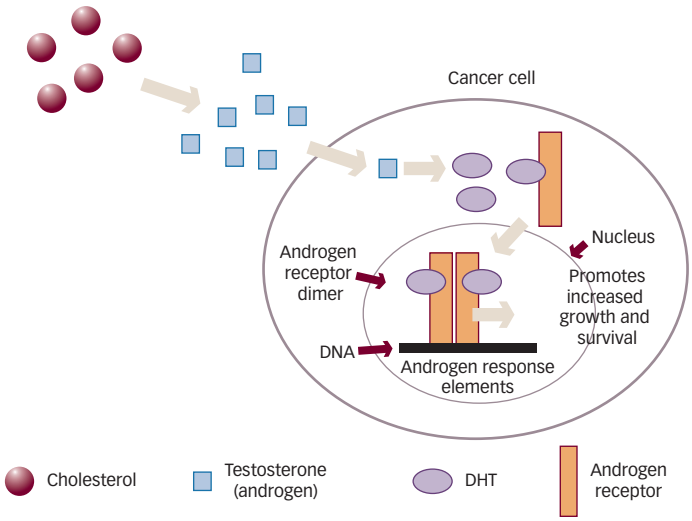
Prostate cancer continues to be a leading cause of cancer-related death worldwide and is the most common malignancy among American men after skin cancer.[1] Based on estimates by the American Cancer Society, approximately 241,740 new cases are expected to be diagnosed and 28,170 men are expected to die from the disease in the US in 2012. Approximately one in six men will be diagnosed with prostate cancer during their lifetime.[1] Although patients with recurrent disease initially respond to androgen deprivation therapy (ADT), most will go on to develop castration-resistant prostate cancer (CRPC) in which the disease becomes refractory to traditional hormone therapies and cancer growth continues despite castrate levels of testosterone. However, this population may still respond to secondary hormonal manipulations and ADT continues to be the gold standard for systemic treatment of men with metastatic disease.[2]

While the five-year survival rate for men with advanced prostate cancer has increased from 69 % in the late 1970s to 100 % in the 2000s,[2] there have traditionally been no successful treatments that improved median overall survival in the subset of patients with CRPC. In the last decade, however, since the approval of docetaxel by the US Food and Drug Administration (FDA) for metastatic CRPC in 2004,[3] there has been a substantial evolution in its treatment, as several drugs introduced in quick succession show efficacy in prolonging survival. In particular, greater understanding of the pathogenesis of advanced disease resulted in the development of effective targeted therapies.

Biology of the Disease—Dependence on Androgen-mediated Signaling

The androgen signaling pathway has recently been found to be critical in both hormone-sensitive prostate cancer and CRPC.[4] Evidence has shown that resistant cancer continues to rely on androgen biosynthesis, its binding to the receptor and consequent uptake in order to progress.[5–7] *Figure 1* presents a simplified disease progression pathway illustrating the conversion of cholesterol to androgen and testosterone. Within cells, the hormones are converted to the more potent dihydrotestosterone (DHT) metabolites, which function as intracellular

Figure 1: Schematic Illustrating the Androgen Pathway Involved in Promoting Tumor Growth



DHT = dihydrotestosterone.

signals operating via the androgen receptor (AR, a ligand-dependent transcription factor), ultimately leading to tumor growth.[8] Studies have demonstrated that 0.5 to 1.0 nM of DHT—the concentration observed in prostatic tissue of castrate patients—is sufficient to activate the AR and androgen-regulated genes and promote cell growth.[9,10] Together, these findings highlight the significant roles both androgen and the AR play in cancer survival in this patient population.

Various molecular mechanisms have been proposed to explain the development of CRPC, which appears to remain dependent on androgen.[11] These include increased expression and/or activity of the AR through gene mutations and upregulation of steroidogenic enzymes such as CYP17, resulting in increased androgen production.[7] AR mutations have been reported in some patients with advanced disease.[12] Some mutations found in CRPC lead to the AR losing its specificity for androgens. As a result, it begins responding to other entities including estrogens, progesterone, and perhaps even antiandrogens.[13]

Gene amplification resulting in AR hyper-responsiveness, enhanced AR signal transduction independent of ligands, and activation of downstream regulatory molecules are also possible mechanisms of resistance.[8,11] Upregulation of nuclear transcription co-activators also leads to AR-mediated gene transcription in the presence of low levels of systemic androgens or with less potent androgens.[14] This androgen signaling pathway and its components have therefore become important targets for therapeutic development.

Recent research suggests that other parallel pathways may also be involved in perpetuating resistance. These include the mitogen-activated protein kinase (MAPK) pathway,[15] the Met pathway,[16] as well as other growth factor pathways that together work to stimulate growth and proliferation. It is therefore likely that no single pathway dominates, but rather that there is a combination of multiple mechanisms of resistance. Moreover, the prostate cancer cells themselves have been shown to stimulate intratumoral steroidogenesis and maintain intratumor androgen at the levels needed for tumor growth.[7]

Current Standard of Care

With the introduction of three new agents in the last two years, the standard of care for CRPC in the US has changed immensely. For a long time, docetaxel was the only therapy available that showed any benefit in survival. However, in 2010, a new chemotherapy agent, cabazitaxel, demonstrated prolonged survival in patients progressing post-docetaxel[17,18] and gained FDA approval. It was followed soon after by sipuleucel-T, an autologous dendritic cell-based immunotherapy cancer vaccine.[19] A further agent, abiraterone acetate, was approved in April 2011.[20,21] MDV3100 and radium-223 are currently in late-stage development and are expected to be approved in the near future. These treatments, including their mechanisms of action, are summarized in *Table 1* and are discussed in greater detail in the following sections.

At present, the optimal sequencing of these new agents in the treatment of CRPC remains unclear. In general, based on experience, most physicians treating metastatic CRPC will begin with sipuleucel-T (for asymptomatic and minimally symptomatic disease) and proceed to docetaxel. This can then be followed by either abiraterone or cabazitaxel.[22] Since abiraterone is administered orally and is more tolerable, patients and clinicians tend to favor this treatment prior to cabazitaxel. As additional therapies such as MDV3100 and radium-223 gain approval, the algorithms used by physicians will continue to evolve.

Novel Agents

Cabazitaxel

Cabazitaxel is a non-cross-resistant microtubule target agent that promotes tubulin assembly. The drug thereby significantly stabilizes microtubules within the prostate, conferring antitumor activity. Preclinical studies showed positive activity of cabazitaxel over docetaxel in some chemotherapy-resistant models.[23] A Phase I trial of cabazitaxel in 25 patients with advanced solid malignancies showed promising outcomes in refractory disease as well as acceptable tolerability.[24] Neutropenia was the main dose-limiting toxicity, with non-hematologic toxicities being mild-to-moderate in severity.

In a pivotal open-label randomized Phase III trial, 755 men with metastatic CRPC, whose disease had progressed with previous hormone therapy, were treated with 10 mg oral prednisone plus either mitoxantrone (n=377) or cabazitaxel (n=378) intravenously every three weeks.[17] Median survival was 15.1 months in the cabazitaxel group versus 12.7 months in the mitoxantrone group ($p<0.0001$). Similarly, progression-free survival was 2.8 months and 1.4 months in the cabazitaxel and mitoxantrone groups, respectively ($p<0.0001$). Again, neutropenia was the major safety issue, with 82 % of subjects receiving cabazitaxel experiencing grade 3 or higher neutropenia. Moreover, there were toxic deaths in 5 % of cabazitaxel patients, leading to the recommendation of prophylactic granulocyte macrophage colony-stimulating factor (GM-CSF) in accordance with American Society of Clinical Oncology guidelines.

Overall, this novel drug demonstrated important improvements to survival in CRPC patients during a time when few options were

Table 1: Therapeutic Agents Recently Approved or in Late-stage Development for Castration-resistant Prostate Cancer

Agent	Class	Indication	Standard Regimen	Mechanism of Action
Approved				
Cabazitaxel	Microtubule inhibitor	For patients with metastatic CRPC in combination with prednisone post-docetaxel	25 mg/m^2 IV every 3 weeks with prednisone 10 mg PO daily for 6 cycles	Stabilizes microtubules
Sipuleucel-T	Autologous cellular immunotherapy	For patients with metastatic CRPC with minimal symptoms	IV doses every 2 weeks for 3 cycles	Boosts the immune system against prostate-specific protein
Abiraterone acetate	CYP17 inhibitor	For patients with metastatic CRPC in combination with prednisone post-docetaxel	1,000 mg PO daily with prednisone 5 mg PO BID for 8 months	Inhibits androgen biosynthesis
In Development				
MDV3100	Small molecule AR antagonist	Not approved yet	160 mg/day PO	Binds to and inhibits the AR
Radium-223	α-emitting radiopharmaceutical	Not approved yet	4 to 6 IV injections of 50 kBq/kg every 4 weeks	Induces double-stranded DNA breaks through irradiation

AR = androgen receptor; BID = twice daily; CRPC = castration-resistant prostate cancer; IV = intravenous; PO = orally.

available.[17] An ongoing Phase III trial is comparing first-line docetaxel with two doses of cabazitaxel (25 or 20 mg/m^2).

Sipuleucel-T

Sipuleucel-T is a therapeutic cancer vaccine that was introduced in 2010 for men with asymptomatic or minimally symptomatic metastatic CRPC. It is an autologous treatment in which peripheral blood mononuclear cells are collected from patients via leukapheresis and processed at an external site. The cells—which include antigen-presenting cells—are activated with a recombinant fusion protein, PA2024, which consists of a prostate antigen, prostatic acid phosphatise, and GM-CSF.[19] The enriched *ex vivo* product is returned and later infused back into the patient where it stimulates the immune defences against the disease.

Following encouraging survival results from small-scale randomized, placebo-controlled studies,[25,26] a Phase III double-blind, multicenter trial was performed with 512 subjects with metastatic CRPC using overall survival as the primary endpoint.[19] Previous studies had used time to progression as the primary endpoint and had shown no significant differences between treatment and control; however, a survival advantage had been observed. In the present study, the sipuleucel-T group demonstrated a survival advantage (relative reduction of 22 % in the risk of death) compared with placebo (hazard ratio 0.78; p=0.03). This corresponded to a 4.1-month difference in median survival (25.8 months with sipuleucel-T versus 21.7 months with placebo). Again, median time to disease progression was not significantly different between the two groups, suggesting that overall survival is a superior endpoint. The therapy was generally well tolerated, with 31.7 % of sipuleucel-T-treated subjects experiencing serious adverse events compared with 35.1 % in the placebo group. Negative effects more commonly observed in the treatment group included chills, fever, and headache.[19] Surprisingly, changes in levels of prostate-specific antigen (PSA) and progression-free survival were not observed, making outcome predictions with sipuleucel-T use particularly challenging.[22]

Abiraterone Acetate

CYP17 (cytochrome P450 17 alpha-hydroxylase) is a steroidogenic enzyme essential in the production of systemic testosterone, contributing to the disease progression pathway through androgen synthesis. Administered orally, abiraterone, selectively and irreversibly inhibits this enzyme, thereby significantly reducing the amount of testosterone in patients.[27] While gonadotropin-releasing hormone (GnRH) agonists and /or antagonists can substantially reduce testosterone levels secreted by the testicles, they are not sufficient in blocking production from the adrenal glands and some prostate cells that continue to synthesize testosterone. Abiraterone suppresses this extragonadal testosterone generation, almost eliminating measurable systemic levels of the male hormone.[28,29] Feedback loop activation of the mineralocorticoid pathway could be mitigated by low dose corticosteroids.

Abiraterone is currently the only FDA-approved hormonal therapeutic option for patients with metastatic CRPC who have progressed following docetaxel.[30] Its approval resulted from the positive findings of several clinical trials. In particular, a Phase III study was conducted that randomized 1,195 docetaxel-refractory CRPC patients to prednisone plus either abiraterone or placebo in a 2:1 ratio.[20] Overall survival was longer in the abiraterone group versus the placebo group (14.8 months versus 10.9 months, respectively; hazard ratio 0.65; p<0.001). The treatment group also demonstrated superior outcomes for all secondary endpoints (time to PSA progression, progression-free survival, and PSA response rate). In general, treatment with abiraterone was well tolerated. Adverse events that were reported more frequently in abiraterone subjects than in those receiving placebo included mineralocorticoid-related effects such as fluid retention (31 %), hypokalemia (17 %), and hypertension (10 %).[20] While this treatment is currently only indicated in the post-docetaxel setting, it is expected to be approved for pre-docetaxel therapy as well, based on recent findings presented this year.[31]

Agents in Development

MDV3100

MDV3100 is an orally administered small molecule AR antagonist that binds to the AR with a higher affinity than previous AR-blocking agents such as bicalutamide. This suppresses AR translocation into the nucleus, recruitment of transcription co-activators, and DNA binding.[32] Following positive results of MDV3100 from an early Phase I/II study,[33] several Phase III clinical trials are currently under way.[34,35] In particular, the AFFIRM (A study evaluating the efficacy and safety of investigational

drug MDV3100 without concurrent prednisone in men with advanced CRPC) trial is examining this agent in patients post-docetaxel. Results illustrate a survival benefit with MDV3100 compared with placebo (18.4 months versus 13.6 months, hazard ratio 0.631; p<0.0001).[36,37] Moreover, MDV3100 met all secondary endpoints (which included radiographic progression-free survival, soft tissue response rate, and time to PSA progression [all p<0.0001]) with statistical significance. Based on these data, the study was halted early and treatment offered to the placebo arm. Overall, MDV3100 demonstrated a favorable safety profile; common side effects consisted of fatigue, diarrhea, and hot flushes; serious adverse events were all lower in the MDV3100 group than in the placebo group. With these promising findings, MDV3100 is expected to receive FDA approval in the near future. A second Phase III trial to evaluate the treatment in chemotherapy-naive patients is currently ongoing.[35]

Radium-223

Compared with the two available β-emitting radiopharmaceutical agents (strontium-89 and samarium-153 EDTMP, used mainly for palliation) radium-223 can induce double-stranded DNA breaks in tumors with less deleterious penetration into surrounding tissues.[2] This α-emitting therapy has been previously studied in Phase I and Phase II trials, where it exhibited minimal toxicity and a trend toward improved survival.[38,39] This led to further research in the Phase III setting, with an estimated primary completion date of October 2012.[40] In particular, radium-223 is being investigated in patients with advanced CRPC and symptomatic bone metastases. Early findings announced in press releases indicate that the primary endpoint of improved overall survival has been met and the tolerability profile is consistent with previous studies.[41] Updated data show that radium-223 improved overall survival by 44 % (hazard ratio 0.695; p<0.0001), corresponding to a median benefit of 3.6 months (14.9 months in patients given treatment versus 11.3 months in those given placebo).[41,42] It was therefore concluded that radium-223 may become a new standard of care for CRPC patients with bone metastases.

Rationale for Combining Therapies

Considering the different modes of action of the various available treatments to target tumor cells in the CRPC patients, it would be sensible to combine therapies with the goal of producing superior results to those obtained with single agents alone. For example, abiraterone works by decreasing androgen production. However, any testosterone that remains in circulation may still trigger AR activity and result in cancer growth. Therefore, the addition of MDV3100 to the regimen may enhance clinical outcomes by acting directly on the AR and blocking any interaction that may lead to adverse downstream signaling. Further research is required to test this and similar hypotheses with complementary products, as well as determine optimal combinations. Challenges may include a more severe toxicity profile and continued safety analyses are needed monitor this. At present, several trials are under way to evaluate different combinations in CRPC, including docetaxel plus abiraterone.[43]

As findings from combination studies begin to emerge, physicians and researchers will develop a better sense of which algorithms may be best suited for their patients as well as of potential safety concerns.

Agents in Earlier Stages of Development

Other androgen synthesis inhibitors (TAK-700) and AR antagonists (ARN-509) are undergoing Phase III development. Novel immunotherapeutic strategies such as ipilimumab, the T-cell checkpoint CTLA-4-inhibiting monoclonal antibody, and Prostvac® (a poxvirus-based vaccine) are undergoing Phase III evaluation. Radioimmunotherapy is undergoing Phase II evaluation for non-metastatic CRPC in the form of a radiolabelled antibody targeting prostate specific membrane antigen. Additionally, cabozantinib, a small molecule tyrosine kinase inhibitor targeting c-Met and vascular endothelial growth factor receptor-2, is undergoing Phase III evaluation based on promising Phase II data.[44] Phase III trials are investigating outcomes of the combination of custirsen (a novel antisense agent against clusterin) and chemotherapeutic agents.

Summary and Conclusion

Several novel targeted therapies were recently introduced—cabazitaxel, sipuleucel-T, and abiraterone acetate—and others are in late-stage development, including MDV3100 and radium-223. This has and will continue to change the face of CRPC treatment, significantly improving overall survival. For the most part, therapeutic development has focused on inhibiting steroidogenesis and any subsequent downstream effects. As the therapies target different aspects of the disease progression pathway, it may be practical to combine complementary agents to optimize results. The optimal sequencing of these agents and biomarkers to predict benefits should be a major focus of research for the future management of CRPC. Exploiting circulating tumor cells and novel modalities to better assess tumor burden is also important. Research into this area, together with a better understanding of the biology and mechanisms of resistance coupled with emerging biomarkers, will help inform management decisions and will ultimately improve clinical outcomes. ■

1. American Cancer Society, Prostate Cancer: What are the key statistics about prostate cancer? Available at: www.cancer.org/Cancer/ProstateCancer/DetailedGuide/prostate-cancer-key-statistics (accessed August 16, 2012).
2. Higano CS, Crawford ED, New and emerging agents for the treatment of castration-resistant prostate cancer, *Urol Oncol,* 2011;29(6 Suppl.):S1–8.
3. US Food and Drug Administration, FDA Approves New Indication for Taxotere – Prostate Cancer, May 19, 2004, Available at: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2004/ucm108301.htm (accessed August 16, 2012).
4. Ruch JM, Hussain MH, Evolving therapeutic paradigms for advanced prostate cancer, *Oncology (Williston Park),* 2011;25:496–504, 508.
5. Locke JA, Guns ES, Lubik AA, et al., Androgen levels increase by intratumoral de novo steroidogenesis during progression of castration-resistant prostate cancer, *Cancer Res,* 2008;68:6407–15.
6. Mohler JL, Gregory CW, Ford OH 3rd, et al., The androgen axis in recurrent prostate cancer, *Clin Cancer Res,* 2004;10:440–8.
7. Montgomery RB, Mostaghel EA, Vessella R, et al., Maintenance of intratumoral androgens in metastatic prostate cancer: a mechanism for castration-resistant tumor growth, *Cancer Res,* 2008;68:4447–54.
8. Attar RM, Takimoto CH, Gottardis MM, Castration-resistant prostate cancer: locking up the molecular escape routes, *Clin Cancer Res,* 2009;15:3251–5.
9. Culig Z, Hoffmann J, Erdel M, et al., Switch from antagonist to agonist of the androgen receptor bicalutamide is associated with prostate tumour progression in a new model system, *Br J Cancer,* 1999;81:242–51.
10. Gregory CW, Johnson RT Jr, Mohler JL, et al., Androgen receptor stabilization in recurrent prostate cancer is associated with hypersensitivity to low androgen, *Cancer Res,* 2001;61:2892–8.
11. Mostaghel EA, Montgomery B, Nelson PS, Castration-resistant prostate cancer: targeting androgen metabolic pathways in recurrent disease, *Urol Oncol,* 2009;27:251–7.
12. Marcelli M, Ittmann M, Mariani S, et al., Androgen receptor mutations in prostate cancer, *Cancer Res,* 2000;60:944–9.
13. Taplin ME, Bubley GJ, Shuster TD, et al., Mutation of the androgen-receptor gene in metastatic androgen-independent prostate cancer, *N Engl J Med,* 1995;332:1393–8.
14. Gregory CW, He B, Johnson RT, et al., A mechanism for androgen receptor-mediated prostate cancer recurrence after androgen deprivation therapy. Cancer Res, 2001;61:4315–9.
15. Mukherjee R, McGuinness DH, McCall P, et al., Upregulation of MAPK pathway is associated with survival in castrate-resistant prostate cancer, *Br J Cancer,* 2011;104:1920–8.

16. Agarwal N, Sonpavde G, Sternberg CN, Novel molecular targets for the therapy of castration-resistant prostate cancer, *Eur Urol,* 2012;61:950–60.
17. de Bono JS, Oudard S, Ozguroglu M, et al., Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial, *Lancet,* 2010;376:1147–54.
18. National Cancer Institute, FDA Approval for Cabazitaxel, June 17, 2010. Available at: www.cancer.gov/cancertopics/druginfo/fda-cabazitaxel (accessed August 16, 2012).
19. Kantoff PW, Higano CS, Shore ND, et al., Sipuleucel-T immunotherapy for castration-resistant prostate cancer, *N Engl J Med,* 2010;363:411–22.
20. de Bono JS, Logothetis CJ, Molina A, et al., Abiraterone and increased survival in metastatic prostate cancer, *N Engl J Med,* 2011;364:1995–2005.
21. National Cancer Institute, FDA Approval for Abiraterone Acetate, July 12, 2011. Available at: www.cancer.gov/cancertopics/druginfo/fda-abirateroneacetate (accessed August 16, 2012).
22. Crawford ED, Flaig TW, Optimizing outcomes of advanced prostate cancer: drug sequencing and novel therapeutic approaches, *Oncology (Williston Park),* 2012;26:70–7.
23. Bissery M, Bouchard H, Riou JF, et al., Preclinical evaluation of TXD25, a new taxoid (abstract 1364), *Proc Am Assoc Cancer Res,* 2000;41:214.
24. Mita AC, Denis LJ, Rowinsky EK, et al., Phase I and pharmacokinetic study of XRP6258 (RPR 116258A), a novel taxane, administered as a 1-hour infusion every 3 weeks in patients with advanced solid tumors, *Clin Cancer Res,* 2009;15:723–30.
25. Higano CS, Schellhammer PF, Small EJ, et al., Integrated data from 2 randomized, double-blind, placebo-controlled, phase 3 trials of active cellular immunotherapy with sipuleucel-T in advanced prostate cancer, *Cancer,* 2009;115:3670–9.
26. Small EJ, Schellhammer PF, Higano CS, et al., Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic, asymptomatic hormone refractory prostate cancer, *J Clin Oncol,* 2006;24:3089–94.
27. Rehman Y, Rosenberg JE, Abiraterone acetate: oral androgen biosynthesis inhibitor for treatment of castration-resistant prostate cancer, *Drug Des Devel Ther,* 2012;6:13–8.
28. Attard G, Reid AH, Yap TA, et al., Phase I clinical trial of a selective inhibitor of CYP17, abiraterone acetate, confirms that castration-resistant prostate cancer commonly remains hormone driven, *J Clin Oncol,* 2008;26:4563–71.
29. Ryan CJ, Smith MR, Fong L, et al., Phase I clinical trial of the CYP17 inhibitor abiraterone acetate demonstrating clinical activity in patients with castration-resistant prostate cancer who received prior ketoconazole therapy, *J Clin Oncol,* 2010;28:1481–8.
30. Beckett RD, Rodeffer KM, Snodgrass R, Abiraterone for the treatment of metastatic castrate-resistant prostate cancer, *Ann Pharmacother,* 2012;46:1016–24.
31. Ryan CJ, Smith MR, de Bono JS, et al., Interim analysis (IA) results of COU-AA-302, a randomized, phase III study of abiraterone acetate (AA) in chemotherapy-naive patients (pts) with metastatic castration-resistant prostate cancer (mCRPC), *J Clin Oncol,* 2012;30(Suppl.): abstract LBA4518.
32. Tran C, Ouk S, Clegg NJ, et al., Development of a second-generation antiandrogen for treatment of advanced prostate cancer, *Science,* 2009;324:787–90.
33. Scher HI, Beer TM, Higano CS, et al., Antitumour activity of MDV3100 in castration-resistant prostate cancer: a phase 1-2 study, *Lancet,* 2010;375:1437–46.
34. Safety and Efficacy Study of MDV3100 in Patients With Castration-Resistant Prostate Cancer Who Have Been Previously Treated With Docetaxel-based Chemotherapy (AFFIRM). Available at: http://clinicaltrials.gov/ct2/show/NCT00974311 (accessed August 16, 2012).
35. A Safety and Efficacy Study of Oral MDV3100 in Chemotherapy-Naive Patients With Progressive Metastatic Prostate Cancer (PREVAIL). Available at: http://clinicaltrials.gov/ct2/show/NCT01212991 (accessed: August 16, 2012).
36. de Bono JS, Fizazi K, Saad F, et al., Primary, secondary, and quality-of-life endpoint results from the phase III AFFIRM study of MDV3100, an androgen receptor signaling inhibitor, *J Clin Oncol,* 2012;30(Suppl.): abstract 4519.
37. Medivation, Medivation and Astellas Announce Positive Results From the Phase 3 AFFIRM Trial of MDV3100 in Prostate Cancer Patients Who Received Prior Chemotherapy. Available at: http://investors.medivation.com/releasedetail.cfm?releaseid=644382 (accessed: August 16, 2012).
38. Nilsson S, Franzén L, Parker C, et al., Bone-targeted radium-223 in symptomatic, hormone-refractory prostate cancer: a randomised, multicentre, placebo-controlled phase II study, *Lancet Oncol,* 2007;8:587–94.
39. Nilsson S, Larsen RH, Fosså SD, et al., First clinical experience with alpha-emitting radium-223 in the treatment of skeletal metastases, *Clin Cancer Res,* 2005;11:4451–9.
40. A Phase III Study of Alpharadin (Radium-223) in Patients With Symptomatic Hormone Refractory Prostate Cancer With Skeletal Metastases (ALSYMPCA). Available at: http://clinicaltrials.gov/ct2/show/NCT00699751 (accessed: August 16, 2012).
41. Algeta, Updated phase III data confirm overall survival benefit of Alpharadin in men with advanced prostate cancer that has spread to the bone, June 4, 2012. Available at: http://www.algeta.com/xml_press_underside.asp?xml=http://cws.huginonline.com/A/134655/PR/201206/1616967.xml&m=34572&s=34686&ss=&d=2012-06-04 (accessed August 16, 2012).
42. Parker C, Nilsson S, Heinrich D, et al., Updated analysis of the phase III, double-blind, randomized, multinational study of radium-223 chloride in castration-resistant prostate cancer (CRPC) patients with bone metastases (ALSYMPCA), *J Clin Oncol,* 2012;30(Suppl.): abstract LBA4512.
43. A Safety Study of Abiraterone Acetate Administered in Combination With Docetaxel in Patients With Metastatic Castration-Resistant Prostate Cancer (mCRPC). Available at: http://clinicaltrials.gov/ct2/show/NCT01400555 (accessed August 16, 2012).
44. Hussain M, Smith MR, Sweeney C, et al., Cabozantinib (XL184) in metastatic castration-resistant prostate cancer (mCRPC): Results from a phase II randomized discontinuation trial, *J Clin Oncol,* 2011;29(Suppl.): abstract 4516.