



Review Article

Novel agents in the management of castration resistant prostate cancer

Shruti Chaturvedi¹, Jorge A. Garcia^{2,3*}

Departments of ¹Internal Medicine, ²Solid Tumor Oncology and ³Urology, Cleveland Clinic, Taussig Cancer Institute and Glickman Urological and Kidney Institute, Cleveland, Ohio 44195, USA

E-mail: garciaj4@ccf.org

*Corresponding author

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Abstract

Prostate cancer (PCa) is a leading cause of cancer mortality in men and despite high cure rates with surgery and/or radiation, 30-40% of patients will eventually develop advanced disease. Androgen deprivation is the first line therapy for standard of care for men with advanced disease. Eventually however all men will progress to castration-resistant prostate cancer (CRPC). Insight into the molecular mechanisms of androgen resistance has led to the development of alternative novel hormonal agents. Newer hormonal agents such as abiraterone, enzalutamide and TOK-001; and the first cancer vaccine, SipuleucelT have been approved for use in men with CRPC. The recognition of the importance of bone health and morbidity associated with skeletal related events has led to the introduction of the receptor activator of nuclear factor kappa-B-ligand inhibitor denosumab. Other molecularly targeted therapies have shown promise in pre-clinical studies, but this has not consistently translated into clinical efficacy. It is increasingly evident that CRPC is a heterogeneous disease and an individualized approach directed at identifying primary involvement of specific pathways could maximize the benefit from targeted therapies. This review focuses on targeted therapy for PCa with special emphasis on therapies that have been Food and Drug Administration approved for use in men with CRPC.

Keywords: Adrenal synthesis inhibition, androgen deprivation, androgen receptor, bone health, castration-resistant prostate cancer, immunotherapy, second-line hormonal therapy

INTRODUCTION

Prostate cancer (PCa) is the second leading cause of cancer mortality in men, with an estimated 238,000 new cases and 29,000 deaths annually in the United States.^[1] Albeit the vast majority of patients with PCa are cured with surgery and/or radiation therapy, more than 30-40% of patients

will eventually progress and develop advanced disease. Although the timing of androgen deprivation therapy (ADT) remains controversial, testosterone suppression (medical or surgical castration) remains the standard of care for men with advanced disease.^[2,3] All men who undergo medical or surgical castration will eventually progress and develop castration-resistant disease. Castration-resistant prostate cancer (CRPC) is often manifested by either a rising of the prostate-specific antigen (PSA), or radiographic or clinical progression in the setting of a testosterone level <50 ng/mL.^[4]

A better understanding of the biology of CRPC and the role of androgen receptor (AR) in this setting has allowed the rapid development of several new compounds that have revolutionized the management of the disease. Novel

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immune compounds, selective adrenal inhibitors, newly engineered AR inhibitors and less toxic radio nucleotides are among the new agents currently Food and Drug Administration (FDA) approved for the management of men with CRPC. Similarly, the recognition of the importance of bone health and prevention of skeletal related events (SREs) has permitted the introduction of the receptor activator of nuclear factor kappa-B-ligand (RANK-L) inhibitor denosumab in different disease settings.

Although the appropriate sequence of treatment and the mechanisms of resistance to the novel AR or adrenal inhibitors remain unknown, the utilization of these agents in clinical practice have clearly translated into a significant palliative and clinical benefit for most patients. This review focuses on targeted therapy for PCa with special emphasis on therapies that have been FDA approved for use in men with CRPC.

ANDROGEN DEPRIVATION THERAPY

Androgen Deprivation Therapy (ADT) has remained the cornerstone of therapy of advanced PCa since Huggins and Hodge demonstrated the favorable impact of androgen deprivation through surgical castration, or estrogens on metastatic PCa.^[2,3] Bilateral orchiectomy was the classic method of suppressing testosterone to castrate levels (<50 ng/mL), but has gone out of vogue since the discovery of equally effective methods of medical castration including luteinizing hormone-releasing hormone (LHRH) agonists and antagonist.^[5] Orchiectomy is irreversible, has adverse psychological consequences and does not allow for intermittent therapy in men with biochemical recurrence after primary definitive therapy. Diethylstilbestrol (DES) was the first agent used as a reversible alternative to orchiectomy in the 1960s and 1970s.^[5] However, effective in suppressing testosterone, it posed unacceptably cardiovascular risks as demonstrated by the Veterans Administration Cooperative Urology Research Group.^[6,7] Despite this, it remained the major alternative to surgical castration until a landmark study showed that the LHRH agonist leuprolide had similar clinical efficacy without the adverse effects (AEs) observed with the use of DES.^[8,9] LHRH agonists cause down regulation of LHRH receptors on prolonged exposure and suppress pituitary luteinizing hormone and follicle-stimulating hormone secretion thereby suppressing testosterone secretion to castrate levels.^[10,11] It should be noted, however, that a transient flare of testosterone occurs within the first 7-10 days after treatment with LHRH.^[12-14] Clinicians should be aware of this phenomenon as a small percentage of PCa patients could develop complications such as urinary obstruction, worsening pain and spinal cord compression.^[15] The flare phenomenon can

be avoided by either simultaneous use of an AR inhibitor such as bicalutamide or the use of this agent alone for few weeks prior to the initiation of LHRH therapy.^[16] LHRH antagonists that directly block gonadotropin-releasing hormone (GnRH) receptors and cause castrate levels of testosterone without an initial flare, have emerged as alternatives to GnRH analogues in advanced PCa.^[17-20] Degarelix, a third-generation, GHRH antagonist is the most extensively studied and widely available agent of this class. In a randomized phase III trial, degarelix was compared to leuprolide in 610 PCa men in need of ADT. There were no differences in the ability to reduce testosterone levels to a castrate state although a faster reduction of testosterone and PSA levels were observed when degarelix was used.^[21,22]

Most patients with advanced PCa have an initial response to ADT, but eventually progress to a castration-resistant state. CRPC refers to rising PSA, radiographic progression or worsening symptoms in the setting of castrate levels of testosterone.^[4,23] Despite of the lack of testosterone, AR remains the major therapeutic target in CRPC. Some of the proposed mechanisms for the development of castration-resistant disease include AR activation in a ligand independent manner, selection of a mutant AR by anti-androgen therapy, AR gene amplification, activating mutations in the AR and selection of pre-existing clones of androgen independent cells that are resistant to apoptosis.^[24-27]

Biochemical as well as clinical responses can be achieved in patients with CRPC upon withdrawal of anti-androgen therapy. This phenomenon has been described with flutamide,^[28] bicalutamide,^[29,30] nilutamide^[31] as well as with DES.^[32] Antiandrogen withdrawal (AAWD) is a cost effective and a mandatory maneuver for men with CRPC prior to initiating subsequent therapy.^[33]

Although only 5-10% of the circulating testosterone is produced by the adrenal glands, adrenal androgens such as dehydroepiandrosterone, dehydroepiandrosterone sulfate and 5-androstenediol can also lead to activation of the wild type AR.^[34,35] In addition, they can be metabolized to dihydrotestosterone.^[36] Ketoconazole is an antifungal agent capable of inhibiting CYP-17 and the enzyme β -11 hydroxylase ultimately leading to the inhibition of early adrenal steroids synthesis. A phase III study (CALGB 9583) investigated the use of AAWD with or without simultaneous ketoconazole and hydrocortisone.^[37] The PSA response was 27% in those who received AAWD and ketoconazole versus 11% in those treated with AAWD alone. The objective response rates were 20% and 2% respectively while no differences in overall survival (OS) were seen. The sequential use of ketoconazole also led to PSA responses in 32% patients

and objective responses in 7%. Adrenal insufficiency is the major limiting AE of this agent hence the need for simultaneous steroid replacement.

NOVEL ORAL HORMONAL AGENTS

Abiraterone acetate

Abiraterone acetate is a novel, selective, irreversible, oral inhibitor of CYP17A1 and 17, 20 hydroxylase that inhibits early adrenal androgen production, peripheral circulation of testosterone and intracrine testosterone production.^[38-42] Initial phase I/II studies confirmed its safety and activity in CRPC with PSA responses >50% and overall response rates ranging from 25% to 60% respectively.^[39,40] Its major toxicities were edema, hypokalemia and hypertension that are attributable to a syndrome of secondary mineralocorticoid excess.^[41,42] A randomized, double blinded, placebo-controlled phase III trial (COU-AA301) compared abiraterone acetate plus prednisone versus prednisone plus placebo in 1195 men with docetaxel refractory metastatic CRPC (mCRPC). The study reported a 14.8 months median OS in the prednisone/abiraterone arm compared with 10.9 months in the prednisone/placebo arm (hazard ratio [HR]: 0.646, $P < 0.0001$). It also showed improved PSA response rate (38% vs. 10%, $P < 0.0001$) and radiographic progression-free survival (rPFS) (5.6 vs. 3.6 months, $P < 0.0001$) in the prednisone/abiraterone group. Nearly 15% patients in the abiraterone arm developed grade 3 and 4 toxicities mainly liver dysfunction, hypokalemia, fluid retention and hypertension.^[42]

Recently, COU-AA302 a randomized, phase III placebo study demonstrated the activity of this compound in men with asymptomatic or minimally symptomatic chemotherapy-naïve mCRPC. The rPFS was significantly greater for those receiving abiraterone acetate compared to that of placebo/prednisone (16.5 vs. 8.3 months; HR: 0.53; $P < 0.001$). Similarly, the PSA and ORR observed in the abiraterone arm was 62 and 24% respectively compared with 36 and 16% in the placebo/prednisone arm ($P < 0.0001$) AEs on this trial were similar to those observed in the prost-chemotherapy setting with no new safety issues of concern. Although there was no statistical difference in the OS (a co-primary endpoint of the study), the use of this agent in this setting has gained momentum. The timing and mechanism of resistance to abiraterone remain unknown and is currently the source of multiple translational studies. Table 1 summarises important trials of novel hormonal agents for the treatment of CRPC.

TAK-700 (Orteronel)

TAK-700 is another novel, selective inhibitor of CYP17A1 that has shown acceptable toxicity and promising activity in phase I/II trials in men with mCRPC.^[43] At doses

of >400 mg twice daily TAK-700 reduced mean testosterone levels to <0.6 ng/dl and resulted in PSA responses >50% in 70% or patients treated with >300 mg twice a day. In a phase II study in men with non-mCRPC and rising PSA, TAK-700 was shown to reduce PSA by 50% in 76% patients and by 90% in 32% patients at the end of 3 months.^[44] Two randomized, double-blind, multicenter phase III trials of TAK-700 are underway. The first, C21004, includes men with chemotherapy naïve mCRPC treated with TAK-700 or placebo (C21004) plus open label prednisone and GnRH analogue therapy. The second (C21005) is a trial of prednisone plus TAK-700 or placebo in men with mCRPC who have progressed on docetaxel. These studies have completed accrual and final analyses are expected for 2014. A preliminary press-release from C21005 has suggested a lack in OS improvement in the octeronel arm.

Enzalutamide

Enzalutamide formerly known as MDV3100 is a thiohydantoin derivative capable of blocking AR. Contrary to bicalutamide, in the setting of AR amplification enzalutamide does not become a ligand to AR. Promising results in a phase I/II dose finding study led to the initiation of two phase III placebo controlled studies - one in chemotherapy naïve patients with CRPC (PREVAIL) and the other in the post chemotherapy setting (AFFIRM).^[45-47] The AFFIRM study showed a median OS was 18.4 months in the enzalutamide versus 13.6 months in the placebo group (HR: 0.63, $P < 0.001$). Enzalutamide was also superior to placebo in all secondary end points including PSA response >50% (54% vs. 2%, $P < 0.001$), soft-tissue response rate (29% vs. 4%, $P < 0.001$), the quality-of-life response rate (43% vs. 18%, $P < 0.001$), the time to PSA progression (8.3 vs. 3.0 months; HR, 0.25; $P < 0.001$), rPFS (8.3 vs. 2.9 months; HR, 0.40; $P < 0.001$) and the time to the first skeletal-related event (16.7 vs. 13.3 months; HR, 0.69; $P < 0.001$). AEs of special interest included fatigue and cardiovascular in nature that occurred in 33 and 6.1% of patients receiving enzalutamide. Less than 2% of patients taking enzalutamide experience liver function test abnormalities. Similarly, <1% of patients receiving enzalutamide experienced seizure activity. The mechanism behind this AE appears to be gamma-aminobutyric acid (GABA) mediated. Several trials evaluating the activity of enzalutamide in the chemotherapy-naïve setting are underway. These efforts will likely result in the label expansion of this agent in this early setting.

IMMUNOTHERAPY

Sipuleucel-T

Sipuleucel-T (Provenge) is another novel agent recently approved by the FDA for the management of men with

chemotherapy-naïve asymptomatic or minimally symptomatic mCRPC. Sipuleucel consists of autologous dendritic cells harvested from the patient and subsequently cultured with a fusion protein consisting of prostatic acid phosphatase (PAP) and granulocyte-macrophage colony-stimulating factor (PAP2024).^[48] These activated dendritic cells are infused back into the patient and appear to be capable of sensitizing naïve T cells to PAP. Two randomized control trials (D9901 and D9902A) with TTP as the primary endpoint were initially carried out. Whereas neither trial met the primary end point, median OS was improved by 4 months in the D9901 study. A pooled analysis of these studies confirmed that treatment with sipuleucel-T leads to a 33% relative risk reduction of death from PCa.^[49] A larger phase III, multicenter randomized controlled trial, was subsequently conducted in 512 men with no symptoms or minimal symptoms from mCRPC. This study demonstrated a 4.1 month improvement in OS (its primary endpoint) as well as a 22.5% reduction in the risk of death (HR: 0.775, $P = 0.03$) in men treated with Sipuleucel-T. The most adverse events (AEs) observed were grade 1 and 2 in nature and included chills,

fever (pyrexia), headache, influenza-such as illness, myalgia, hypertension, hyperhidrosis and groin pain. Most of these AEs occurred within 1 day after infusion and resolved within 1-2 days. Interestingly, neither PSA response nor radiological improvements were observed with the use of this agent.^[50] These observations have raised the question about appropriate patient selection and the need for better methods to monitor response when using immune agents. A number of clinical trials are evaluating the combination of Sipuleucel-T with agents capable of producing PSA and objective responses such as abiraterone and/or enzalutamide. The results of these studies could lead to a greater utilization of this immune approach in men with CRPC.

BONE TARGETED THERAPY

Bone is the most common site of metastases in men with PCa. While less than 20% of men initially present with bone involvement, the vast majority of them (> 80%) will eventually develop bone disease.^[4,51-52] Metastases from PCa generally appear osteoblastic on radiographs; however, increases in both osteoblastic and osteolytic activity have been implicated

Table 1: Summary of trials of novel hormonal agents for the treatment of CRPC

Study	Drug	Control	Clinical setting	Primary outcomes	Safety
Abiraterone acetate					
COU-AA-301; de Bono <i>et al.</i> 2011 ^[42]	Prednisone (5 mg b.d.)/ abiraterone acetate (1000 mg/day)	Prednisone (5 mg b.d.)/ placebo	Phase III; mCRPC (previous doc); N=1195 (2:1 ratio)	OS, 15.8 versus 11.2 months; HR, 0.74 ($P<0.0001$)	Grade 3/4 hypokalemia (4.4% vs. 0.8%); grade 3/4 hypertension (1.3% vs. 0.3%); liver function Abnormalities (11.3% vs. 8.9%); cardiac disorders (15.9% vs. 11.7%)
COU-AA-302; Ryan 2012	Prednisone (5 mg b.d.)/ abiraterone acetate (1000 mg/day)	Prednisone (5 mg b.d.)/ placebo	Phase III; chemotherapy naïve mCRPC; N=1088	OS, 35.3 months versus 30.1 months; HR, 0.79 ($p= ns$); cPFS, 16.5 months versus 8.3 months; HR 0.53 ($P<0.0001$)	Grade 3/4 hypertension (3.9% vs. 3.0%); grade 3/4 hypokalemia (2.4% vs. 1.9%); elevated alanine transaminase (5.4% vs. 0.7%); elevated aspartate aminotransferase (3.0% vs. 0.9%)
Enzalutamide					
Scher <i>et al.</i> 2012 ^[47]	Enzalutamide (30-600 mg/day)	None	Phase I/II; mCRPC; N=140, pharmacokinetics, dose finding	PSA response, 56%; TTP (PSA), 32 weeks; TTP (radiology), 47 weeks	Grade P3 AEs: fatigue (11%), anemia (3%); maximum tolerated dose 240 mg/day
AFFIRM ^[61]	Enzalutamide (160 mg/day)	Placebo	Phase III; CRPC (previous doc); N=1199 (2:1 ratio)	OS, 18.4 versus 13.6 months; HR 0.63 ($P<0.0001$)	Grade>3 AEs: cardiac disorders (0.9% vs. 2%); fatigue (6% vs. 7%); seizure (0.6% vs. 0%); liver function abnormalities (0.4% vs. 0.8%)
PREVAIL ^[60]	Enzalutamide	Placebo	Phase III; chemotherapy naïve CRPC	OS, PFS	
TAK-700 (orteronel)					
Dreicer <i>et al.</i> 2010 ^[43]	TAK-700 or prednisone/ TAK-700	None	Phase I/II; mCRPC; N=32	Pharmacokinetics, PSA response (P300 mg), 80%; PSA 90% decline (P300 mg), 27%	Fatigue ($n=17$; 3 grade P3), nausea ($n=11$; 1 grade 3), constipation ($n=10$), anorexia ($n=9$), vomiting ($n=7$, 2 grade P3), AE-related discontinuations ($n=6$)
CS21004	Prednisone/ TAK-700	Prednisone/ placebo	Phase III; chemotherapy naïve mCRPC; N=1454	OS, PFS	
CS21005	Prednisone/ TAK-700	Prednisone/ placebo	Phase III; mCRPC (previous chemotherapy); N=1083	OS	

CRPC: Castration-resistant prostate cancer; mCRPC: Metastatic castration-resistant prostate cancer; HR: Hazard ratio; PFS: Progression-free survival; OS: Overall survival; NR: Not reached; PSA: Prostate-specific antigen; TTP: Time-to-progression; AEs: Adverse effects

Table 2: Summary of investigations of bone targeted agents for prostate cancer

Study	Drug	Control	Clinical setting	Primary outcomes	Secondary outcomes	Safety
Zoledronic acid						
Saad (2002 and 2004) ^[70,71]	Zoledronic acid (4 mg q3w or 8 mg to 4 mg q3w)	Placebo	Phase III; mCRPC; N=643	SRE at 15 months (zol 4 mg vs. zol 8/4 mg vs. placebo), 33.2% versus 38.5% versus 44.2% ($P=0.021$ for zol 4 mg vs. placebo); SRE at 24 months, 38% versus 41% versus 49% ($P=0.028$ for zol 4 mg vs. placebo)	Time to first SRE 488 versus 363 days, HR 0.68 ($P=0.009$), uNTX decreased by 70% in zoledronic acid arm, increased pain scores in placebo arm	Renal function deterioration during infusion (15.2% vs. 20.7% vs. 11.5%), grade 3 creatinine increase (3.3% vs. 2.3% vs. 1.0%), myalgia (24.8% vs. 24.3% vs. 17.8%), fever (20.1% vs. 22.0% vs. 13.0%)
Denosumab						
Fizazi <i>et al.</i> 2011 ^[64]	Den (120 mg q4w, s.c.)	Zol (4 mg q4w, i.v.)	Phase III; bisphosphonate naive mCRPC; N=1904	Time to first SRE, 20.7 versus 17.1 months: HR, 0.82 ($P=0.0002$, non-inferiority; $P=0.008$, superiority)	uNTx reduction 84% versus 69% ($P<0.0001$), OS 19.4 versus 19.8 months, no difference in TTP	Time to first and subsequent SREs, rate ratio, 0.82 ($P=0.008$); uNTx reduction, 84% versus 69% ($P<0.0001$); OS, 19.4 versus 19.8 months; TTP, 8.4 versus 8.4 months
Smith <i>et al.</i> 2012 ^[72]	Den 120 mg q4w	Placebo	Phase III; non-metastatic CRPC; N=1432	Bone metastasis-free survival, 29.5 versus 25.2 months: HR, 0.85 ($P=0.028$)	Time to first bone metastasis 33.2 versus 29.5 months, HR, 0.84 ($P=0.032$); OS, similar between arms	ONJ, 5% versus 0%; hypocalcaemia, 2% versus <1%
Radium-223 chloride (Alpharadin)						
ALSYMPCA Parker (2011 and 2012) ^[67,68]	Rad (50 kBq/kg i.v. q4w)	Placebo	Phase III; mCRPC with bone metastases; N=922 (2:1 ratio)	OS, 14.9 versus 11.3 months: HR, 0.695 ($P=0.00007$)	Time to first SRE 15.6 versus 9.8 months, HR 0.658 ($P=0.00037$)	Nausea (34% vs. 32%); diarrhea (22% vs. 13%); constipation (18% vs. 18%); vomiting (17% vs. 13%); grade 3/4 AEs: neutropenia (2.2% vs. 0.7%); thrombocytopenia (6.3% vs. 2.0%)

mCRPC: Metastatic castration-resistant prostate cancer; SRE: Skeletal related event; HR: Hazard ratio; uNTx: Urinary N-terminal telopeptide; OS: Overall survival; TTP: Time-to-progression; CRPC: Castration-resistant prostate cancer; AEs: Adverse effects; ALSYMPCA: Alpharadin in symptomatic prostate cancer

in tumor invasion of bone.^[53] These metastases disrupt the balance of bone formation (mediated by osteoblasts) and bone resorption (mediated by osteoclasts) and increase the incidence of SREs including pathologic fractures, spinal cord compression and radiation to the bone in addition to causing significant pain. These SREs significantly impair patient's quality of life, shorten survival and pose a formidable health care burden.^[53-56] Biomarkers of bone turnover (alkaline phosphatase and N terminal telopeptide) are independent predictors of disease progression, SREs and death.^[57-59] Thus, prevention and management of bone metastases and SREs is a priority to reduce PCa related morbidity and mortality. Until recently zoledronic acid was the most commonly used agent in the CRPC setting. Although its use has been expanded to the bone loss prevention and hormone responsive setting, to date no prospective level 1 data has demonstrated its benefit in early settings. Newer agents such as Denosumab and Radium-223 have recently been approved. Table 2 summarizes studies of bone targeted agents in prostate cancer.

Denosumab

Osteoclast activation is a pivotal step in tumor invasion and proliferation in bone. RANK-L binds to its cognate

receptor (RANK) and leads to osteoclast differentiation, activation and signaling.^[60] *In vitro* experiments have shown that culturing PCa cells with osteoclasts increases RANK-L production.^[61] *In vivo* inhibition of RANK-L leads to immediate and extensive osteoclast apoptosis.^[62] Furthermore, decreases in progression of bone metastases with RANK-L inhibition has been demonstrated in animal studies.^[63] Denosumab is a humanized monoclonal antibody against RANK-L^[62] that is approved in the USA and Europe for the prevention of bone loss in patients on ADT and for the prevention of SREs in patients with bone metastases. A phase III study of 1904 patients showed that Denosumab was superior to zoledronic acid in delaying the time to first SRE (20.7 vs. 17.1 months, $P = 0.008$).^[64] A subsequent study evaluating denosumab in over 1400 men with non-metastatic castrate-resistant disease demonstrated that treatment with denosumab increased bone metastasis free survival time by 4.2 months compared to placebo ($P = 0.028$). Although no OS benefit was observed, this data coupled with the previous phase III trial have solidified the position of Denosumab in men with CRPC. The obvious question of cost versus benefit ratio in the non-metastatic setting remains hotly debated in the PCa community. In routine clinical practice

monthly denosumab is reserved for men with mCRPC. A different dose and schedule of denosumab is also utilized in men receiving testosterone suppression therapy with the goal of bone loss prevention. When evaluating the AE profile of this agent, hypocalcemia and osteonecrosis of the jaw (ONJ) remain the most common AEs observed. Patients receiving bisphosphonates or RANK-L inhibitors should be encouraged to follow a healthy diet, regular exercise and to continue with their daily calcium and vitamin D supplementation.

Radionuclide therapy

Radionuclides are bone-seeking radio-isotopes that are systemically administered but selectively taken up in areas of rapid bone turnover, such as metastatic foci. The earlier agents were beta-emitters. Strontium-89 has been shown to be at least as effective as external beam radiotherapy in palliating bone pain with significant pain relief in 46-88% patients.^[65-67] The major limitation of its use is significant myelosuppression. Alpha radiation, on the other hand, allows the deposition of high energy radiation over a much smaller distance than beta or gamma emitting radioisotopes thereby minimizing damage to bone marrow and other organs. Radium-223 (Alpharadin) is a calcium mimetic and alpha emitter that was evaluated in men with mCRPC with symptomatic bone metastases. The Alpharadin in with symptomatic mCRPC and bone disease Symptomatic Prostate Cancer phase III study randomized patients in a 2:1 fashion to receive 6 monthly intravenous injections at 4-week intervals of Radium-223+ best supportive care (BSC) or placebo + BSC. Patients with visceral disease were excluded from the trial.

The median OS was 14 versus 11.2 months in favor of Radium-223 (HR: 0.69; 95% confidence interval [CI], 0.552-0.875; $P = 0.0018$). The time to first SRE was also in favor of the Radium-223 arm (13.6 vs. 8.4 months respectively (HR: 0.61; 95% CI, 0.46-0.80; $P = 0.0004$)).^[68] Radium-223 was well-tolerated. Grade 3 AEs included anemia, neutropenia and thrombocytopenia in 11, 2 and 4% of patients respectively. Less than 2% of patients receiving Radium-223 experienced GI AEs. G3 bone pain was similar in both arms (18 and 23% respectively).

Based on these results, Radium-223 was recently FDA approved in the US for men with symptomatic mCRPC with predominance of bone metastases. Bone is the main target of this novel compound, as such selection of patients with other sites of disease outside the bone compartment is critical to optimize the management of their disease. An ongoing phase I/II study evaluating the MTD, safety and clinical efficacy of Radium-223 in combination with docetaxel-based

chemotherapy is underway. Preliminary safety data suggest that the combination of these two compounds is feasible but required dose reductions to minimize AEs. Other ongoing trials include the combination of Radium-223 with either abiraterone acetate or enzalutamide. Retreatment with Radium-223 after a full completion of front-line treatment (6 cycles) remains experimental.

The significant increase in FDA approved therapeutic agents for use in patients with mCRPC has added to clinicians' armamentarium but has also made clinical decision making more complex.

Patients with asymptomatic or minimally symptomatic patients with mCRPC and good performance status and no prior docetaxel therapy are great candidates for agents such as Sipuleucel-T or Abiraterone acetate. Those with prior docetaxel therapy may consider second-line chemotherapy or agents such as enzalutamide or abiraterone acetate. Docetaxel should be offered to all patients with symptomatic mCRPC and acceptable functional status. Currently, radium-223 could also be utilized in this setting, especially in those patients with predominant and symptomatic bone disease.

Existing guidelines also recommend treatment to promote bone health (example calcium, vitamin D) in patients with CRPC and either denosumab or zoledronic acid in patients with bony metastases to prevent fractures and SREs.^[69]

CONCLUSIONS

Investigation into the molecular mechanisms underpinning tumor growth and progression has drastically changed developmental therapeutics for PCa. Newer hormonal agents such as abiraterone, enzalutamide and TOK-001; bone targeted agents such as bisphosphonates, denosumab and Radium-223; and a cancer vaccine, Sipuleucel T have been approved for clinical use in men with CRPC. While several other molecularly targeted therapies have shown promise in pre-clinical studies, this has not consistently translated into clinical efficacy. Given the molecular complexity of the AR signaling cascade, targeting multiple pathways simultaneously may yield the most benefit in achieving sustained and clinically meaningful responses. It is increasingly evident that CRPC is a heterogeneous disease and patient subgroups characterized by the primary involvement of specific pathways of cancer progression are likely to exist. A more personalized and biologic approach, by identifying specific molecular subtypes, could maximize the benefit from any of the new targeted compounds. Identification of immune monitoring techniques is required to define the true biologic impact of immunotherapy.

With several new developments on the horizon, the priority remains to quickly discard marginal therapies and identify the most promising ones to expeditiously evaluate them in phase III clinical trials with standardized, clinically-meaningful endpoints.

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AUTHOR'S PROFILE

Dr. Shruti Chaturvedi: Department of Internal Medicine, Cleveland Clinic, Taussig Cancer Institute and Glickman Urological and Kidney Institute, Cleveland, USA

Dr. Jorge A Garcia: Departments of ¹Medicine, and ²Solid Tumor Oncology, Cleveland Clinic, Taussig Cancer Institute and Glickman Urological and Kidney Institute, Cleveland, USA



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