

Evolving treatment approaches for the management of metastatic castration-resistant prostate cancer – role of radium-223

Deborah Mukherji¹
Imane El Dika¹
Sally Temraz¹
Mohammed Haidar²
Ali Shamseddine¹

¹Department of Hematology/
Oncology, ²Department of Nuclear
Medicine, American University
of Beirut Medical Center, Beirut,
Lebanon

Abstract: Radium-223 is a first-in-class alpha particle-emitting radiopharmaceutical approved for the treatment of bone metastatic castration-resistant prostate cancer. Radium-223 is administered intravenously with no requirement for complex shielding and specifically targets areas of bone metastasis. In a randomized placebo-controlled Phase III study, treatment with radium-223 was shown to improve overall survival, time to skeletal-related events, and health-related quality of life. Apart from radium-223, the cytotoxic chemotherapy agents docetaxel and cabazitaxel, androgen biosynthesis inhibitor abiraterone acetate, novel anti-androgen enzalutamide, and immunotherapy sipuleucel-T have also been shown to improve survival of men with advanced prostate cancer in Phase III trials. This review will outline current treatment approaches for advanced prostate cancer with a focus on the role of radium-223 in changing treatment paradigms.

Keywords: Alpharadin, alpha-emitting radionuclide, bone metastasis

Introduction

Radium-223 dichloride (radium-223, Xofigo [previously known as Alpharadin; Bayer AG, Leverkusen, Germany]) is a novel alpha-emitting radionuclide recently approved for the treatment of castration-resistant prostate cancer (CRPC) metastatic to bone. Radium-223 administered intravenously forms a complex with hydroxyapatite, selectively targeting areas of increased bone turnover associated with bone metastasis.¹ Beta-emitting radiopharmaceuticals such as strontium-89 and samarium-153 have been used in the past for palliation of bone pain associated with diffuse metastatic disease; however, duration of response is relatively short with no evidence of an impact on survival.^{2,3}

In a randomized Phase III study (ALSYMPCA [ALphradin in SYMptomatic Prostate CAncer Patients]), treatment with radium-223 significantly prolonged survival of patients with bone metastatic CRPC compared to placebo, resulting in approval for use in this setting in the United States in May 2013.⁴ This review will outline current treatment approaches for advanced prostate cancer with a focus on the role of radium-223 in changing treatment paradigms.

Data for this review were compiled using MEDLINE/PubMed, American Society of Clinical Oncology (ASCO), and European Society of Medical Oncology (ESMO) abstracts published before February 2014. The search terms included “castrate resistant prostate cancer”, “radium-223”, “Alpharadin”, “abiraterone”, “enzalutamide”, “cabazitaxel”, and “sipuleucel-T”. Information regarding ongoing clinical trials was obtained using the United States National Institute of Health’s online resource clinicaltrials.gov. Only articles published in English were considered.

Correspondence: Deborah Mukherji
Department of Hematology/Oncology,
American University of Beirut Medical
Center, PO Box: 11-0236, Riad El Solh,
Beirut 1107 202, Lebanon
Tel +961 135 0000
Email dm25@aub.edu.lb

Existing and emerging treatment options for CRPC

The treatment of advanced prostate cancer is rapidly evolving; patients are living longer with better quality of life despite a diagnosis of castration-resistant disease.⁵ Apart from radium-223, the cytotoxic chemotherapy agents docetaxel and cabazitaxel, androgen biosynthesis inhibitor abiraterone acetate, novel anti-androgen enzalutamide, and immunotherapy sipuleucel-T have also been shown to improve survival of men with CRPC in randomized Phase III trials (see Table 1).^{6–10} Table 2 summarizes currently available treatment options for asymptomatic CRPC and symptomatic CRPC in the first-, second-, and third-line settings.

Cytotoxic chemotherapy

Docetaxel chemotherapy became the standard of care for the treatment of CRPC in 2004 following the publication of two randomized trials showing a survival advantage over mitoxantrone.^{10,11} Three artificial treatment spaces then emerged in prostate cancer drug development: pre-docetaxel, docetaxel combinations, and post-docetaxel. Despite promising signals in Phase II studies, attempts to combine docetaxel with novel therapeutics have been unsuccessful to date. Negative results have been announced for large Phase III trials

combining docetaxel with the endothelin receptor antagonist atrasentan,¹² the tyrosine kinase inhibitor dasatinib,¹³ and the antiangiogenic agents bevacizumab,¹⁴ lenalidomide,¹⁵ and aflibercept.¹⁶

Drug development in the pre- and post-docetaxel settings has been more successful (Table 1). Cabazitaxel is a novel taxane cytotoxic chemotherapy shown to improve survival in men with CRPC post-docetaxel compared to second-line mitoxantrone.⁶ Treatment with cabazitaxel is associated with significant myelosuppression with relatively high rates of febrile neutropenia reported in the Phase III TROPIC study. Data from expanded-access programs have shown that, with experience and appropriate use of growth factor support, toxicity is manageable with good quality of life outcomes.¹⁷

Targeting androgen receptor signaling

The androgen receptor (AR) signaling pathway remains a key driver of disease progression in CRPC.^{18,19} The peripheral conversion of circulating adrenal androgens and de novo intratumoral androgen synthesis are mechanisms leading to continued AR signaling; however, activation of this pathway may also be ligand-independent.^{20–22} Preclinical data suggest that, in addition to direct cytotoxic effects, taxanes such as

Table 1 Systemic treatment options for advanced prostate cancer showing survival benefit in randomized studies

Drug and mechanism of action	Patient population and intervention	Median survival	Reference
Abiraterone, CYP17-inhibitor	n=1,196, CRPC progressing after docetaxel. Abiraterone plus prednisone versus placebo plus prednisone.	15.8 versus 11.2 months (HR 0.74, 95% CI 0.64–0.86, $P<0.001$)	de Bono et al ⁷
	n=1,088, CRPC, asymptomatic or minimally symptomatic, docetaxel naïve. Abiraterone plus prednisone versus placebo plus prednisone.	35.3 versus 30.1 months (HR 0.75, 95% CI 0.61–0.94, $P=0.01$)	Ryan et al ²⁵
Enzalutamide, second generation antiandrogen	n=1,199, CRPC progressing after docetaxel. Enzalutamide versus placebo.	18.4 versus 13.6 months (HR 0.63, 95% CI 0.53–0.75, $P<0.001$)	Scher et al ⁸
	n=1,717, CRPC, asymptomatic or minimally symptomatic, docetaxel naïve. Enzalutamide versus placebo.	Estimated 32.4 versus 30.2 months (HR 0.70, 95% CI 0.59–0.83, $P<0.001$)	Beer et al ²⁷
Docetaxel, cytotoxic chemotherapy	n=1,006, CRPC. Docetaxel plus prednisone 3-weekly versus docetaxel plus prednisone weekly versus mitoxantrone plus prednisone.	19.2 versus 16.3 months (HR 0.76, 95% CI 0.62–0.94, $P<0.001$)	Tannock et al ¹⁰
Cabazitaxel, cytotoxic chemotherapy	n=755, CRPC progressing after docetaxel. Cabazitaxel plus prednisone versus mitoxantrone plus prednisone.	15.1 versus 12.7 months (HR 0.70, 95% CI 0.59–0.83, $P<0.001$)	de Bono et al ⁶
Radium-223, alpha-emitting radio nucleotide	n=922, CRPC after docetaxel or unfit for docetaxel. Radium-223 versus placebo.	14.9 versus 11.3 months (HR 0.70, 95% CI 0.55–0.86, $P<0.001$)	Parker et al ⁴
Sipuleucel-T, immunotherapy	n=512, CRPC, docetaxel naïve. Sipuleucel-T versus placebo.	25.8 versus 21.7 months (HR 0.78, 95% CI 0.61–0.98)	Kantoff et al ⁹

Abbreviations: CI, confidence interval; CRPC, castration-resistant prostate cancer; HR, hazard ratio.

Table 2 Systemic treatment options for patients with metastatic castration-resistant prostate cancer progressing after LHRH and antiandrogen therapy

Asymptomatic or minimally symptomatic CRPC	Symptomatic CRPC first-line	CRPC second-line (post-docetaxel)	Third-line and further treatments
Abiraterone*	Docetaxel*	Cabazitaxel*	Consider clinical trial participation, eg, cabozantinib Cabazitaxel Enzalutamide Abiraterone
Sipuleucel-T*	Abiraterone*	Abiraterone*	
Enzalutamide*	Enzalutamide*	Enzalutamide*	
Docetaxel*	Radium-223, in patients not fit for docetaxel*	Radium-223*	Abiraterone
Treatment options with no proven survival benefit <ul style="list-style-type: none"> • Estrogens • Ketoconazole • Dexamethasone Consider clinical trial participation	Consider clinical trial participation	Consider clinical trial participation	Docetaxel retreatment (Phase II data)
		Treatment options with no proven survival benefit <ul style="list-style-type: none"> • Mitoxantrone • Estrogens • Samarium • Strontium 	

Note: *Treatments with level I evidence.

Abbreviations: CRPC, castration-resistant prostate cancer; LHRH, luteinizing-hormone-releasing hormone.

docetaxel and cabazitaxel may also act via inhibition of AR nuclear translocation.²³

Abiraterone acetate (Zytiga; Janssen Biotech Inc, Horsham, PA, USA) is an oral inhibitor of CYP17A1, a key enzyme in the testosterone biosynthesis pathway. The use of single-agent abiraterone leads to a rebound increase in luteinizing hormone, hence the development of abiraterone for use in combination with medical or surgical castration.²⁴ The addition of low-dose glucocorticoid resulted in normalization of mineralocorticoid levels and an improvement in blood pressure control in early-phase studies, leading investigators to recommend that abiraterone should be used with prednisone in further clinical trials. Abiraterone 1,000 mg daily plus prednisone has been approved for use in the pre- and post-docetaxel setting for CRPC following two Phase III studies demonstrating superiority over prednisone plus placebo (Table 1).^{7,25}

Enzalutamide (Xtandi; Astellas Pharma Inc., Tokyo, Japan) is an oral androgen receptor antagonist that binds to the androgen receptor more avidly than first generation anti-androgens.²⁶ The Phase III AFFIRM study, which randomized patients with metastatic CRPC who had progressed after docetaxel chemotherapy to enzalutamide 160 mg daily versus placebo, showed a significant survival benefit associated with enzalutamide treatment.⁸ Enzalutamide has recently been shown to improve both radiographic progression-free survival and overall survival (OS) versus placebo prechemotherapy in CRPC, with approval in this setting anticipated in 2014.²⁷ A potential advantage of enzalutamide over androgen biosyn-

thesis inhibitors such as abiraterone is the fact that concurrent steroids are not required; however, approximately 30% of patients in each arm of the AFFIRM study received concurrent corticosteroid treatment.⁸

Immunotherapy

The approval of sipuleucel-T (Provenge; Dendreon, Seattle, WA, USA) for the treatment of prostate cancer in April 2010 saw the first antigen-specific immunotherapy to be approved for cancer treatment. Preclinical studies demonstrated that dendritic cells loaded with an antigen–cytokine fusion protein consisting of prostatic acid phosphatase (PAP) and granulocyte-macrophage colony-stimulating factor (GM-CSF) induced strong cellular immune responses in vivo to tumors and tissues expressing PAP.²⁸ Based on these preclinical observations, sipuleucel-T was developed for clinical use, consisting of autologous dendritic cells loaded with the human PAP–GM-CSF fusion protein.

Sipuleucel-T is individually manufactured for each patient, which involves harvesting peripheral-blood mononuclear cells and their ex vivo incubation with the chimeric protein linking GM-CSF to PAP. Three intravenous infusions are given over a 4-week period. In a Phase III trial involving 512 patients with minimally symptomatic CRPC, median OS was 25.8 months in the group treated with sipuleucel-T compared with 21.7 months in the placebo group (unadjusted hazard ratio [HR] for death in the sipuleucel-T group 0.77; 95% confidence interval [CI] 0.61–0.97, $P=0.02$).⁹

Bone-targeted therapy

Bone metastases are a major cause of prostate cancer-specific morbidity and mortality. The treatment and prevention of skeletal related events (SREs) in prostate cancer has the potential to impact both symptoms and survival in advanced disease. Bisphosphonates such as zoledronic acid and the novel receptor activation of nuclear factor kappa-B (RANK) ligand inhibitor denosumab (Xgeva; Amgen, Thomas Oaks, CA, USA) are commonly used in combination with other forms of systemic therapy for CRPC.

RANK signaling is a potent stimulus for osteoclast proliferation and bone resorption. Denosumab is a fully humanized monoclonal antibody targeting RANK-ligand that has recently been shown to be superior to zoledronic acid in preventing or delaying SREs in patients with bone metastases from CRPC.²⁹ A large double-blind Phase III noninferiority study randomized 1,904 patients to denosumab 120 mg subcutaneously monthly or zoledronic acid 4 mg intravenously monthly. The primary endpoint was time to SRE as defined by pathological fracture, radiotherapy to bone, surgery to bone, or spinal cord compression. Denosumab was shown to be superior to zoledronic acid for prevention of SRE (median time to SRE 20.7 months versus 17.1 months; HR =0.82; $P=0.008$).²⁹ A Phase III placebo-controlled study also demonstrated that denosumab significantly improved bone metastasis-free survival in men with CRPC (29.5 versus 25.2 months; HR =0.85;

95% CI: 0.73–0.98; $P=0.028$); however there was no improvement in OS.³⁰

Radium-223: mechanism of action

Radium-223 is an alpha particle-emitting radionuclide that delivers tumor cell-damaging radiation directly to sites of bone metastasis. Radium forms complexes with the bone mineral hydroxyapatite as a natural calcium mimetic, preferentially targeting areas of increased bone turnover associated with metastatic disease.³¹ Radium-223 is administered intravenously in chloride salt solution, decaying to stable lead-207 in a six-stage process. Four alpha particles are emitted per decay, accounting for approximately 95% of the total radiation energy emitted.³²

Alpha particles (composed of two protons and two neutrons) have more than 7,000 times the mass of beta particles, resulting in high linear energy transfer and significantly more biological damage over a very short range (Figure 1). The relatively long range of beta-emitting radiopharmaceuticals may cause significant bone marrow suppression and limit repeated administration.³³ The track length of the alpha particle is 0.10 mm (five to ten cell diameters) compared with 0.6 mm for samarium-153 and 2.4 mm for strontium-89, limiting damage to normal tissues.¹ Preclinical studies performed in rats demonstrated a significant bone marrow-sparing advantage with radium-223 compared with strontium-89.³⁴

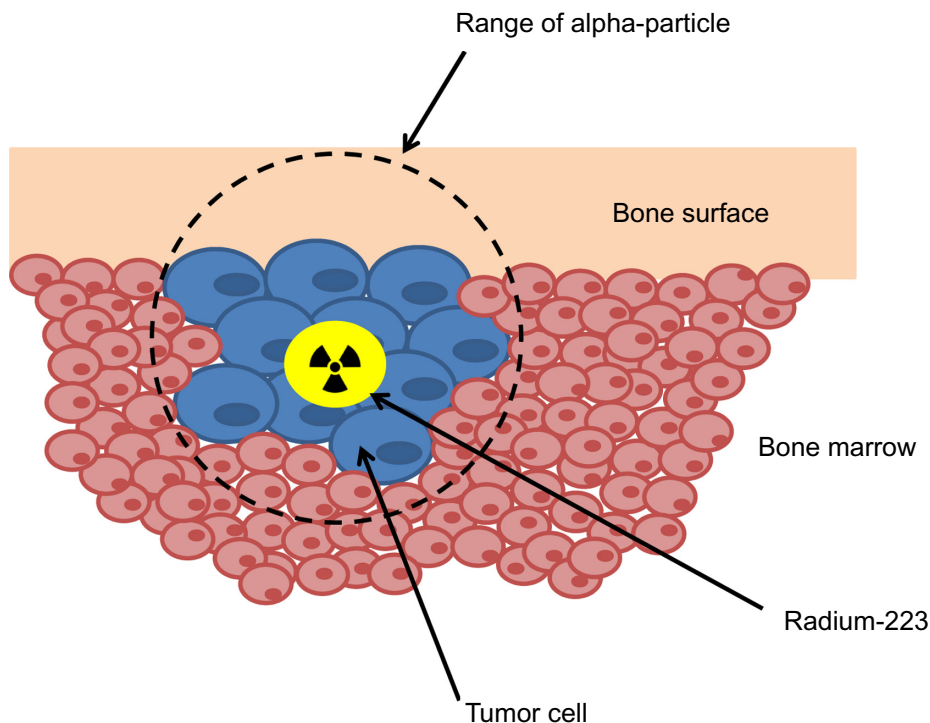


Figure 1 Mechanism of action of radium-223.

In an experimental bone metastasis model in nude rats, radium-223 was found to be selectively concentrated in bone compared with soft tissues with a dose-dependent increase in symptom-free survival observed.³⁵

Radium-223 is rapidly cleared from the blood following intravenous injection. In a Phase I pharmacokinetic and biodistribution study, 60% of injected radioactivity was sequestered in bone metastasis within 4 hours and the highest absorbed radiation doses were to the osteogenic cells, red bone marrow, and intestinal wall. Radium-223 is not metabolized by the body and excretion is predominately fecal; renal excretion is less than 5%.^{36,37}

Radium-223 is administered using conventional nuclear medicine equipment on an outpatient basis with few radiation protection limitations recommended post-therapy, since the activity administered is considerably lower than the levels administered in standard diagnostic nuclear medicine studies. In patients treated in the Phase I study, dose rates from patients were typically less than 2 $\mu\text{Sv/h/MBq}$ on contact and averaged 0.02 $\mu\text{Sv h}^{-1} \text{MBq}^{-1}$ at 1 minute immediately following administration.³⁸

Radium-223: efficacy and safety

Early-phase clinical development of radium-223 has been reviewed in detail.³⁹ A randomized Phase II study of radium-223 in patients with CRPC and symptomatic bone metastasis showed a significant improvement in serum alkaline phosphatase (ALP) and delayed time to prostate specific antigen progression, and an improved median overall survival at 2 years.^{40,41} The subsequent Phase III ALSYMPCA study randomized 921 patients in a 2:1 ratio to receive six 4-weekly intravenous injections of radium-223 (50 kBq/kg) or placebo. Eligible patients had progressive symptomatic CRPC with two or more bone metastasis on bone scintigraphy scan and no evidence of visceral disease. Patients randomized within this study had either received or were deemed unfit to receive docetaxel chemotherapy. Recruitment took place from June 2008 to February 2011 and the study was stopped in June 2011 on the recommendation of an independent data monitoring committee after a planned interim analysis showed a significant improvement in overall survival in the patients who received radium-223 compared with placebo.

The two arms of the study were well-balanced in terms of patient characteristics with a median age of 71 years. In both the group of patients treated with radium-223 and those treated with placebo, 57% had received prior docetaxel chemotherapy. In an updated analysis, median overall survival was 14.9 months in the radium-223 group and 11.3 months in the placebo group

(HR 0.70; 95% CI 0.58–0.83; $P < 0.001$). The survival benefit associated with radium-223 was consistent across all subgroups irrespective of factors including baseline ALP level, bisphosphonate use, or prior docetaxel treatment.⁴

Key secondary endpoints of the study included time to first SRE, time to ALP progression, and time to prostate-specific antigen progression. Time to first SRE was significantly prolonged in the group receiving radium-223 (15.6 months versus 9.8 months; HR 0.66; 95% CI 0.52–0.82; $P < 0.001$). In particular, radium-223 was effective in significantly reducing the rate of spinal cord compression (3% versus 6%), pathological fracture (4% versus 7%), and need for external beam radiation therapy (23% versus 27%) compared to placebo.⁴²

Radium-223 was generally well tolerated with fewer adverse events occurring in patients treated with radium-223 compared with placebo (all adverse events 93% versus 96%; grade 3 or 4 adverse events 56% versus 62%). The investigators considered there to be no clinically meaningful differences in the frequency of hematological adverse events between the two groups; however, it should be noted that 6% of patients treated with radium-223 developed grade 3 or 4 thrombocytopenia compared with 2% of patients in the placebo group. Only one grade 5 hematologic adverse event was considered possibly related to radium-223 treatment; a patient passed away after developing thrombocytopenia, pneumonia, and hypoxia. Radium-223 was not associated with significant myelosuppression; grade 3 or 4 neutropenia occurred in 3% of patients treated with radium-223 compared with 1% of patients in the placebo group. Recently reported follow-up data at 1.5 years showed no increased incidence of second primary cancers, aplastic anemia, or myelodysplasia associated with radium-223 therapy in this cohort.⁴³ Of the nonhematologic adverse events potentially related to radium-223, diarrhea was more commonly observed in the experimental group; however, this was generally low-grade and manageable (25% in patients treated with radium-223 compared to 15% in the placebo group).⁴

Implications for enhanced patient care, improved quality of life

Data from the ALSYMPCA study suggest that, in addition to prolonging survival, treatment with radium-223 is also associated with an improvement in pain and health-related quality of life. Fewer patients in the radium-223 group required opiate medication for pain relief (36% versus 50%) and fewer patients reported pain as an adverse event (50% versus 62%). In the subgroup of patients not requiring opiates at baseline, median time to opiate use was significantly prolonged in the

Table 3 Radium-223 clinical trials

ClinicalTrials.gov identifier	Status	Study	Phase	Design
NCT01934790	Recruiting	Re-treatment Safety of Radium-223 Dichloride in Castration-resistant Prostate Cancer With Bone Metastases	I,II	Open-label safety
NCT00667199	Completed	Study of Radium-223 for the Palliation of Painful Bone Metastases in (HRPC) Patients	II	Double-blind safety/efficacy
NCT01798108	Completed	Dose Escalation Study of Radium-223 Dichloride in Patients With Advanced Skeletal Metastases	I,II	Open-label safety
NCT00699751	Ongoing	A Phase III Study of Radium-223 Dichloride in Patients With Symptomatic Hormone Refractory Prostate Cancer With Skeletal Metastases (ALSYMPCA)	III	Double-blind randomized
NCT01106352	Recruiting	A Study of Alpharadin® With Docetaxel in Patients With Bone Metastasis From Castration-Resistant Prostate Cancer (CRPC)	I,II	Open-label safety/efficacy
NCT02043678	Not open	Radium-223 Dichloride and Abiraterone Acetate Compared to Placebo and Abiraterone Acetate for Men With Cancer of the Prostate When Medical or Surgical Castration Does Not Work and When the Cancer Has Spread to the Bone, Has Not Been Treated With Chemotherapy and is Causing no or Only Mild Symptoms	III	Double-blind randomized
NCT01070485	Not applicable	A Study of Alpharadin® in Breast Cancer Patients With Bone Dominant Disease no Longer Considered Suitable for Hormone Therapy	I,II	Open-label safety/efficacy
NCT02023697	Not open	Standard Dose Versus High Dose and Versus Extended Standard Dose Radium-223 Dichloride in Castration-resistant Prostate Cancer Metastatic to the Bone	II	Open-label safety/efficacy
NCT02034552	Recruiting	A Randomized Open-label Phase IIa Study Evaluating the Efficacy and Safety of Radium-223 Dichloride in Combination With Abiraterone Acetate or Enzalutamide in Subjects With CRPC Who Have Bone Metastases	II	Open-label safety/efficacy
NCT01618370	Recruiting	Radium(223) Dichloride (Alpharadin) in Castration-Resistant (Hormone-Refractory) Prostate Cancer Patients With Bone Metastases	III	Prospective open-label safety
NCT00748046	Completed	Alpharadin™ Safety and Dosimetry With HRPC That Has Metastasized to the Skeleton	I	Pharmacokinetics/dynamics
NCT00459654	Completed	A Placebo-controlled Phase II Study of Bone-targeted Radium-223 in Symptomatic Hormone-refractory Prostate Cancer	II	Double-blind efficacy
NCT00337155	Completed	A Dose Finding Study of Radium-223 for Prostate Cancer Patients With Bone Metastases	II	Double-blind efficacy
NCT01565746	Ongoing	Safety, Biodistribution, Radiation Dosimetry and Pharmacokinetics Study of BAY88-8223 in Japanese Patients	I	Open-label safety
NCT01833520	Recruiting	Phase I Dose Escalation of Monthly Intravenous Ra-223 Dichloride in Osteosarcoma	I,II	Open-label safety/efficacy
NCT01929655	Recruiting	Japanese BAY88-8223 Monotherapy Phase II Study	II	Open-label safety/efficacy

radium-223 group compared with placebo (HR 0.62; 96% CI 0.46–0.85). Treatment with radium-223 significantly prolonged median time to external-beam radiation therapy for bone pain (HR 0.67; 95% CI 0.53–0.85).⁴⁴

A significantly higher percentage of patients who received radium-223 compared to placebo had a meaningful improvement in quality of life as measured by the FACT-P (functional assessment of cancer therapy – prostate) questionnaire (defined as an increase ≥ 10 points) during study drug administration (25% versus 16%; $P=0.02$).⁴

Conclusion, place in therapy

Radium-223 is a first-in-class alpha particle-emitting radiopharmaceutical shown to prolong overall survival and

improve health-related quality of life in bone metastatic CRPC. In the randomized Phase III ALSYMPCA study, radium-223 was evaluated in a cohort of patients who had progressed following docetaxel chemotherapy or who were considered unfit for docetaxel treatment. In this study, 57% of patients had received prior docetaxel chemotherapy, and it should be noted that the mechanism of action of radium-223 with specific targeting of bone metastatic disease does not preclude its use when any other systemic treatment has failed.⁴⁵ The key question that will determine the place of radium-223 in the sequencing of therapy for CRPC will be the safety of combining this treatment with other survival-prolonging drugs such as abiraterone, enzalutamide, and cabazitaxel. Despite the fact that clinically significant

myelosuppression was not observed in the patients treated in the ALSYMPCA study, heavily pretreated patients with poor bone marrow reserve may be at risk of significant toxicity associated with radium-223 as a single agent or in combination with other systemic therapies. Several combination studies are ongoing in prostate cancer and other tumor types (Table 3); however, this strategy is not currently recommended outside clinical trials. Another question is the use of radium-223 in patients with both bone and visceral metastasis; if the combination of radium-223 with other systemic therapies proves to be safe and effective, this may become a future standard of care.

At present, radium-223 can be considered for all patients with symptomatic bone-only metastatic disease,⁴⁶ particularly those with poor performance status who are unfit for cytotoxic chemotherapy.

Disclosure

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