



The Contemporary Use of Radium-223 in Metastatic Castration-resistant Prostate Cancer

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Abstract

Radium-223 dichloride (radium-223) was approved for the treatment of patients with castration-resistant prostate cancer (CRPC) and symptomatic bone metastases in the United States and Europe in 2013. This followed a reported overall survival benefit for patients treated with radium-223 and best standard of care (BSoc) when compared with placebo and BSoc in the ALpharadin in SYMptomatic Prostate CAncer (ALSYMPCA) trial. At that time, docetaxel was the standard first-line choice for patients with metastatic CRPC (mCRPC). Since then, the treatment landscape has changed dramatically with new hormonal agents (abiraterone and enzalutamide) considered to be the first-line choice for many patients. The optimal patient profile for radium-223 in the modern setting, and its best use either in sequence or in combination with other approved agents are unclear, with few definitive guidelines available. This article reports on the views of a group of urologists and medical oncologists experienced in treating patients with mCRPC with radium-223 in routine clinical practice. The aim is to provide an overview of the current use of radium-223 in the treatment of patients with mCRPC, and to discuss best practices for patient selection and on-treatment monitoring. Where agreement was reached, guidance on the optimal use of radium-223 is provided.

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Introduction

The majority (90%) of patients with castration-resistant prostate cancer (CRPC) will develop bone metastases, which are associated with symptomatic skeletal events (SSEs), impaired quality of life, and reduced survival.¹⁻³ The development and progression of bone

metastases involves the interaction between tumor cells and cells of the bone microenvironment in a vicious cycle that disrupts the balance between osteolytic and osteoblastic activity and interferes with physiologic skeletal remodeling.^{4,5} First, there is an important increase in osteolysis, which is crucial for the seeding of cancer cells

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in the bone. Next, there is an abnormal bone formation owing to the release of cytokines from bone matrix and tumor cells that promote osteoblast differentiation and activity.

Radium-223 dichloride (radium-223), a targeted alpha therapy, was approved in 2013 for the treatment of patients with metastatic CRPC (mCRPC) exclusively with symptomatic bone metastases but without visceral disease and limited lymphadenopathy. This was based on data from a phase III trial in which patients randomized to radium-223 and best standard of care (BSoC) demonstrated longer survival compared with those randomized to placebo and BSoC.⁶ Radium-223 is 1 of 6 survival prolonging agents currently approved for the treatment of mCRPC. The others are the taxane-based chemotherapies, docetaxel⁷ and cabazitaxel,⁸ the new hormonal therapies, abiraterone⁹⁻¹¹ and enzalutamide,^{12,13} and the immunotherapy, sipuleucel-T (not used outside of the United States).¹⁴ Evidence-based treatment guidelines provide recommendations for radium-223 use in the mCRPC setting.¹⁵⁻¹⁷ The optimal patient profile for radium-223, and the best use of the agent either in sequence or in combination with other approved agents is however, unclear, with few expert consensus opinions available.^{18,19}

This article reports on the views of a group of urologists and medical oncologists from Europe, Israel, and Canada experienced in treating patients with mCRPC in routine clinical practice. The aim is to provide an overview of the current use of radium-223 in the treatment of mCRPC and to discuss best practices for patient selection and on-treatment monitoring. Where agreement was reached, guidance is provided on the contemporary use of radium-223.

Overview of Radium-223, a Targeted Alpha Therapy

Mode of Action

Radium-223, a bone-seeking calcium mimetic, forms hydroxyapatite complexes during bone mineralization in areas of high osteoblast activity and increased bone turnover around prostate cancer metastatic lesions.²⁰⁻²² Radium-223 decays to emit predominantly high energy alpha particles over a short range (< 1 mm), leading to cytotoxicity through the production of predominantly unrepairable DNA double strand breaks in nearby tumor and cells forming the cancer microenvironment.²⁰⁻²³ By contrast, beta particle-emitting radionuclides have a comparatively lower energy than radium-223, resulting in less effective DNA damage, and a longer range and higher penetration, leading to higher exposure and toxicity to more distant normal myeloproliferative cells.²³⁻²⁵ Unlike radium-223, which has demonstrated a survival benefit in mCRPC, beta particle emitting radionuclides have shown activity exclusively in relation to bone pain palliation; furthermore, their recent use has diminished.²⁵

Clinical Development

In the pivotal phase III trial (ALpharadin in SYMptomatic Prostate Cancer [ALSYMPCA]), 921 patients with histologically confirmed progressive mCRPC and predominant symptomatic bone metastases (patients with visceral disease or lymph node metastases > 3 cm in the short-axis diameter were excluded) were randomly assigned (2:1) to receive 6 injections of radium-223, 50 kBq/kg (55 kBq/kg following National Institute of Standards and Technology update in 2016) with BSoC or to receive placebo with BSoC.⁶ Patients had received prior docetaxel (57%), or were unfit for docetaxel, had declined

docetaxel, or were unable to receive docetaxel for other reasons (43%). Median overall survival (co-primary endpoint) was longer (14.9 vs. 11.3 months; hazard ratio [HR], 0.70; 95% confidence interval [CI], 0.58-0.83; $P < .001$) in patients receiving radium-223 and BSoC compared with those receiving placebo with BSoC.⁶ Time to first SSE (secondary endpoint) was longer in the radium-223 arm (HR, 0.66; 95% CI, 0.52-0.83; $P < .001$).^{6,26} The short- and long-term safety profile (co-primary endpoint) was favorable, with low rates of myelosuppression,^{6,27-29} and meaningful improvements in quality of life measures recorded in patients in the radium-223 arm.³⁰ Based on these findings, radium-223 was approved for the treatment of patients with mCRPC, symptomatic bone metastases, and no known visceral metastatic disease.

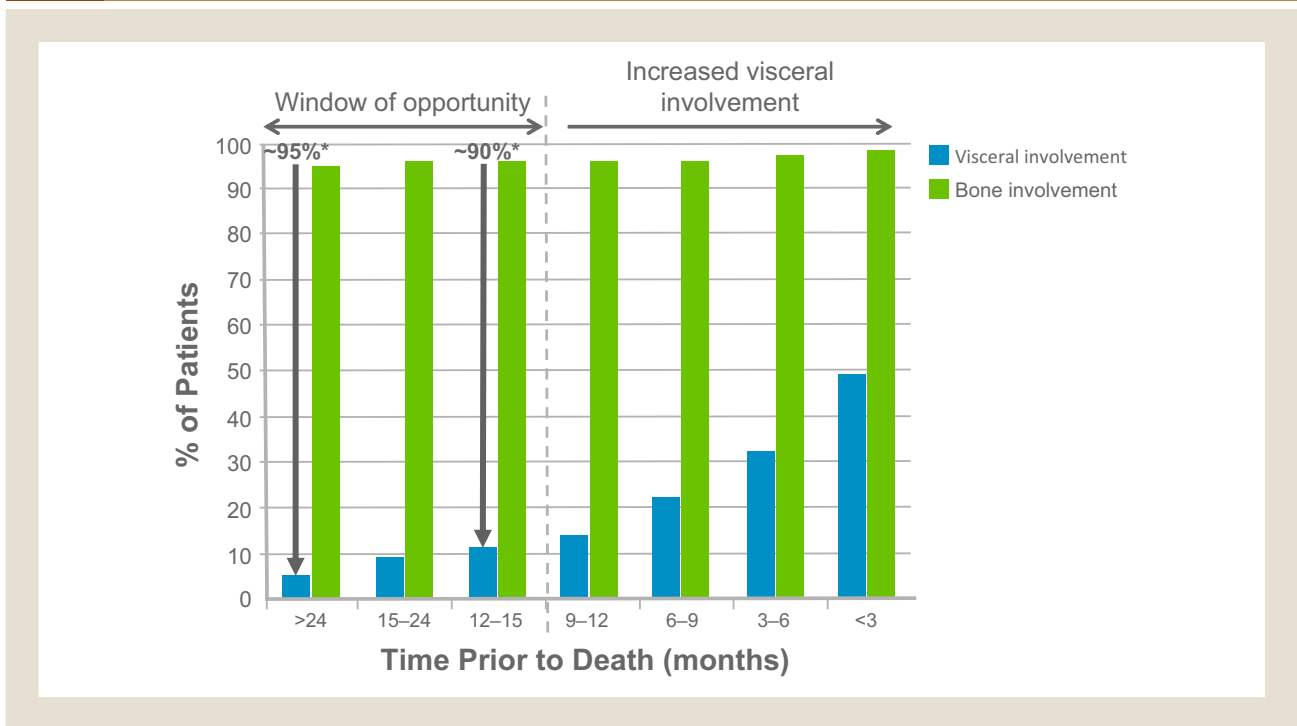
A recent single-arm phase IIIb international early access program (iEAP) reported no new safety concerns for radium-223 when administered to patients with mCRPC and symptomatic or asymptomatic bone metastases in routine clinical practice.^{31,32} In subgroup analyses of this study, radium-223 appeared to be more effective and was equally well-tolerated when given concomitantly with abiraterone and/or enzalutamide.³¹ It has also been shown that radium-223 can be safely combined with bone-supportive agents including denosumab and bisphosphonates, and external beam radiation therapy.^{6,31,33,34} In a further exploratory analysis, overall survival was reported to be longer in patients receiving radium-223 with concomitant denosumab compared with those receiving radium-223 without denosumab.³¹

Contemporary Use of Radium-223

Who Is the Optimal Patient for Radium-223?

The radium-223 label and current prostate cancer treatment guidelines offer little insight into which patients might receive the most benefit from treatment in current clinical practice.^{15,16,35,36} When it was first used in the clinic, particularly in EAPs, a proportion of patients (32%-46%) discontinued radium-223 after 1 to 4 cycles.^{37,38} Most patients enrolled in these programs were quite advanced in their disease course, were heavily pretreated, and were unlikely to benefit from any further systemic anti-cancer treatment. Most had already received chemotherapy, abiraterone or enzalutamide, and other anti-cancer agents. However, the timing and pattern of metastatic spread in patients with CRPC reveals a window of opportunity for the use of radium-223 much earlier prior to the onset of visceral disease (Figure 1).³⁹ The majority (90%) of patients with CRPC will develop bone metastases and no visceral disease, and are therefore potential candidates for radium-223 treatment.

Baseline factors including those related to levels of lactate dehydrogenase (LDH), prostate-specific antigen (PSA), alkaline phosphatase (ALP), hemoglobin, pain, and Eastern Cooperative Oncology Group performance status may be useful in stratifying patients with better prognosis and therefore, those who are earlier in their disease course.^{31,37,38,40} In post hoc analyses, patients with good prognostic factors have been shown to be more likely to complete 6 cycles of radium-223 and, consequently, derive the most benefit from receiving radium-223.^{37,38} In relation to symptoms, the definition of 'symptomatic' used in the ALSYMPCA study (regular use of analgesic medication [paracetamol to opioid analgesics] or treatment with external beam radiation therapy required for cancer-related bone pain within the previous 12 weeks)⁶ is considered by many clinicians to have been too broad. There is a

Figure 1 Prevalence of Visceral and Bone Metastases Over Time; Window of Opportunity for Radium-223. *Patients With Bone Only Metastases

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view that it is the presence of bone-predominant disease that is the more important factor, with symptoms having less importance in treatment selection. Therefore the use of radium-223 in patients with asymptomatic bone metastases might also be beneficial. In a subgroup analysis of the radium-223 iEAP, outcomes for patients with asymptomatic and symptomatic disease were investigated.³¹ The frequency of reported adverse events was similar in both subgroups. Overall survival (HR, 0.486; 95% CI, 0.325-0.728) and time to first SSE (HR, 0.328; 95% CI, 0.185-0.580) were longer in radium-223-treated patients with asymptomatic compared with symptomatic disease.³² However diagnosis of symptoms can be difficult, as pain is usually underreported by patients and often recorded by physicians as either present or absent. Many patients with bone metastases may have symptoms that they do not relate to pain. For example, a recent large survey conducted by the International Prostate Cancer Coalition showed that many patients with skeletal metastases report increasing difficulty in walking and a reduction in the ability to perform everyday activities (<https://www.menwhospeakup.com/index.php>). Patients may also develop asthenia, anorexia, or even cachexia, which can be related to bone metastases burden and progression.

Level 1 evidence indicates the use of radium-223 in patients with CRPC and symptomatic bone metastases (no visceral disease). Although there is currently an absence of level 1 evidence, there was consensus that the majority of patients with mCRPC and predominant bone metastases may be candidates for treatment before the onset of visceral disease. For

example, patients with bone-predominant mCRPC who are earlier in their disease course may benefit from radium-223 treatment.

In What Treatment Sequence Should Radium-223 Be Used?

For a long time, docetaxel was the only systemic treatment option with proven survival benefit for mCRPC. Subgroup analyses from the ALSYMPCA trial showed an overall survival benefit for radium-223 irrespective of prior docetaxel use.⁴¹ In further exploratory analyses, docetaxel administered following radium-223 appeared to be feasible and well-tolerated with no detrimental effects on overall survival reported.⁴²

However, new hormonal agents currently are considered as first-line options in patients with asymptomatic or mildly symptomatic mCRPC.^{15,18} Consequently, the treatment sequence for mCRPC has changed, moving docetaxel and radium-223 after abiraterone and/or enzalutamide when these agents are used as first-line treatment. In patients progressing on first-line new hormonal agents (with no evidence of visceral disease), for those whose disease is symptomatic, radium-223 would be an appropriate second-line choice. Radium-223 with concomitant abiraterone or concomitant enzalutamide (administered at the discretion of the treating physician), has been found to be effective in patients with symptomatic bone metastases in an expanded access setting, and, in the iEAP, in patients with symptomatic or asymptomatic disease.^{31,43} Ongoing randomized clinical trials including Evaluation of Radium-223

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dichloride in combination with Abiraterone in CRPC (ERA-223) (NCT02043678) and Prostate Cancer Consortium in Europe trial III (PEACE III) (NCT02194842) are investigating the first-line combination of radium-223 with abiraterone or enzalutamide in patients with asymptomatic/mildly symptomatic mCRPC, and will provide supporting data for the optimal positioning and combination of radium-223 in the treatment paradigm.

Radium-223 product information, treatment guidelines, and some experienced clinicians do not exclude the use of radium-223 in first-line treatment of some patients with mCRPC and symptomatic bone metastases (no visceral disease).^{15,18,35,36,44} Radium-223 may also be considered for some patients (those with good performance status) as third- or fourth-line treatment options. With no supporting level 1 data from clinical trials, the optimal position of radium-223 in the current treatment paradigm is not established, and decisions as to the timing of its use are left largely to the clinical judgment of the treating physician (Figure 2).

There is currently no level 1 evidence to establish an optimal sequence position for radium-223. Despite this, there was, however, consensus that early administration of radium-223 to patients with predominant bone metastases (and no visceral disease) progressing on first-line treatment (abiraterone or enzalutamide) maybe be considered as an option. However, equally, administration of radium-223 in later lines of treatment may be a suitable and beneficial option for some patients

prior to the onset of visceral disease. Data from the ongoing randomized trials are required before recommendations can be made for administering radium-223 in combination with new hormonal therapies.

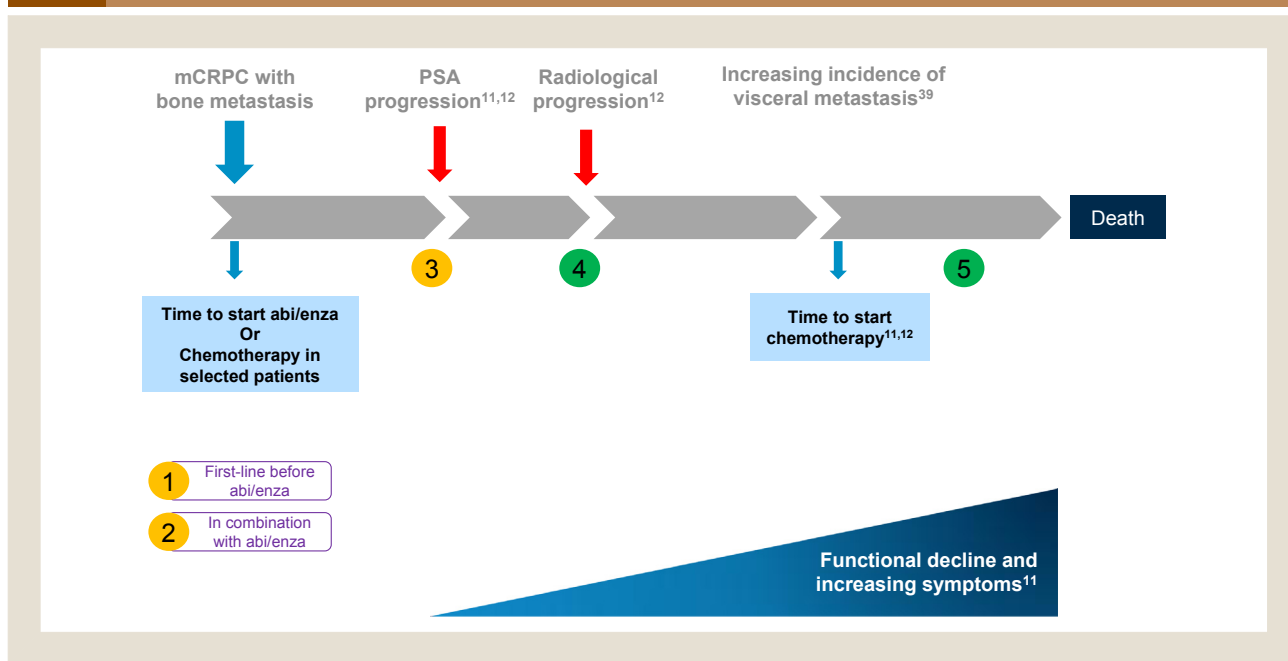
What Monitoring Should Be Performed for Patients Receiving Radium-223?

In general, regular on-treatment monitoring of patients with mCRPC is recommended.^{18,44} This would include clinical and laboratory assessments such as blood counts (neutrophil, platelet, and hemoglobin), assessment of pain and pain medication, Eastern Cooperative Oncology Group performance status, serum markers (PSA, LDH, and ALP), and imaging.

Which Biomarkers Might Be Useful for Monitoring Patients Receiving Radium-223?

Rising PSA levels, and particularly short PSA doubling time, may indicate tumor growth. However, in general, cautious interpretation of PSA data is recommended, as a flare phenomenon has been described following the initiation (first 2-3 months) of chemotherapy and treatment with new hormonal therapies.⁴⁵⁻⁴⁸ PSA expression has been shown to be regulated by the androgen/androgen-receptor axis.^{49,50} Thus, changes in PSA levels can indicate a tumor response to androgen-receptor targeting, for example, by new hormonal therapies.^{9,51} Consequently, PSA

Figure 2 Summary of Possible Positions for Radium-223 in the Treatment Sequence for mCRPC. Supporting Level 1 Evidence is Colored Green. Opinion-only Is Colored Amber. 1. Opinion of Some Clinicians in Patients With Bone Predominant Disease; 2. Data From Ongoing Large Phase III Trials ERA-223 (NCT02043678) and PEACE-3 (NCT02194842) of Radium-223 in Combination With First-line New Hormonal Agents Are Expected; 3. Opinion of Some Clinicians to Add Radium-223 to Abiraterone or Enzalutamide Following PSA Progression on First-line New Hormonal Agents; 4. Phase III Data Support Radium-223 Following First-line Chemotherapy. Preferred Optimal Position by opinion Is Following Radiologic Progression on First-line New Hormones; 5. Phase III Data Support Radium-223 Following First-line Chemotherapy. Opinion Is that it May Be Beneficial to Some Patients With Predominant Bone Metastases (No Visceral Disease) and Comparatively Good Performance Status Who Had Not Previously Received Radium-223



Abbreviations: abi = abiraterone; enza = enzalutamide; mCRPC = metastatic castration-resistant prostate cancer; PSA = prostate-specific antigen.

Table 1 Timing of Assessments for Patients With mCRPC Receiving Radium-223

	Baseline	3 Months	6 Months	Follow-up	Every Cycle
Biomarkers					
Total ALP	+	+	+	+	(+)
PSA	+	(+)	+	+	
LDH	+	+	+	+	+
Imaging					
Bone scintigraphy ^a	+	–	+	–	
CT scan ^a	+	(+)	+	+	
Axial MRI	+	(+)	(+)	(+)	
Other					
Clinical symptoms	+	+	+	+	+
Hematologic parameters	+	+	+	+	+

Recommendations agreed by roundtable discussion at the meeting: + = recommended; (+) = if clinically indicated; – = not routinely recommended.

Abbreviations: ALP = alkaline phosphatase; CT = computed tomography; LDH = lactate dehydrogenase; mCRPC = metastatic castration-resistant prostate cancer; MRI = magnetic resonance imaging; PSA = prostate-specific antigen.

^aBone scintigraphy + CT scans can be replaced with MRI if available.

increases while on treatment with abiraterone or enzalutamide may indicate treatment resistance.

Bone-related markers, for example, bone-specific ALP (a marker of osteoblastic activity), are also reported to be important prognostic factors in patients with mCRPC and bone metastases.^{52,53} In some studies, serum ALP levels appeared to be a more clinically relevant biomarker than PSA in patients with prostate cancer with bone metastases.^{54,55} The mode of action of radium-223 impacts both on tumor growth and tumor-induced pathologic osteoblastic bone growth, and would suggest a primary effect on serum ALP levels.²² In early studies, changes in ALP levels appeared to be a marker of radium-223 effects.^{33,56} In the pivotal phase III study, radium-223 treatment significantly prolonged time to increase in total ALP (tALP) levels, and a higher proportion of patients showed a tALP response ($\geq 30\%$ decrease from baseline) compared with placebo.⁶

Exploratory analyses from the phase III study investigated the effect of radium-223 on changes in tALP, PSA, and LDH levels.⁴⁰ Radium-223 treatment led to a rapid and sustained decrease in tALP levels from baseline through treatment and follow-up compared with placebo (where tALP levels increased during the study). At week 12 (after 3 radium-223 cycles), 87% of patients had a tALP decrease from baseline compared with 23% of patients receiving placebo ($P < .001$). Furthermore, patients receiving radium-223 who experienced a confirmed tALP decline at week 12 had a longer overall survival than those who did not (HR, 0.45; 95% CI, 0.34-0.61).⁴⁰ In contrast, radium-223 had a relatively modest effect on PSA kinetics, with 27% of patients showing a PSA decline at week 12 compared with 14% in the placebo group ($P = .160$).⁴⁰ Similar findings on ALP were reported in the radium-223 iEAP.⁵⁷

Baseline serum LDH levels were also reported to be prognostic for survival in patients with mCRPC.⁴⁰ In the phase III study, radium-223 also had a significant effect on LDH kinetics compared with placebo, with an LDH decline at week 12 reported in 51% of patients treated with radium-223 compared with 34% of those

receiving placebo ($P = .003$). Furthermore, patients treated with radium-223 who experienced a confirmed LDH decline at week 12 survived longer than those without a confirmed decline (HR, 0.55; 95% CI, 0.42-0.73).⁴⁰ It was concluded that without current predictive markers, ALP or LDH changes could be assessed dynamically over the radium-223 treatment course.

In summary, PSA is not a reliable marker for radium-223 treatment. The value of ALP as a biomarker for radium-223 requires further validation. There are also several factors to be considered when proposing the use of a candidate biomarker for monitoring radium-223 treatment efficacy. First, it is important to be aware of flare phenomena, which can occur despite the patient showing a good response to treatment by other parameters. Second, it is important not to stop radium-223 treatment for increases in ALP or PSA alone, as currently neither are validated as markers of progression for radium-223. Finally, it is important to educate patients on their expectations with regard to radium-223 and PSA levels, so as not to increase patient anxiety with unnecessary and sometimes conflicting information on serum biomarker levels.

It was agreed that currently there are no validated biomarkers for monitoring radium-223 efficacy in everyday clinical practice. PSA is not a useful surrogate for monitoring radium-223 efficacy, but changes in ALP dynamics may prove to be more useful. It was agreed that biomarkers should be regularly assessed in patients receiving radium-223 for information purposes and used in the context of other assessments to establish clinical progression (summarized in Table 1).

Which Imaging Techniques Should Be Used for Monitoring Patients Receiving Radium-223?

Imaging methods for patients with mCRPC and bone metastases are summarized in Table 2.

Data on the best imaging methods for monitoring patients on radium-223 are currently lacking. In addition, imaging was not mandated in the ALSYMPCA study.⁶ A number of phase I and II clinical trials with imaging integral to the primary objective are

Table 2 Imaging Techniques in mCRPC With Bone-predominant Metastases

Technique	Advantages	Limitations
^{99m} Tc bone scan	Only technique that can identify areas of: <ul style="list-style-type: none"> Highest bone turnover (may indicate metastases)⁵⁸ Radium-223 accumulation⁵⁸ 	<ul style="list-style-type: none"> Low specificity⁵⁸ Negative scan not sufficient to exclude metastases⁵⁹ Flare phenomenon⁴⁴
¹⁸ F-NaF PET	<ul style="list-style-type: none"> Greater sensitivity than bone scan¹⁵ Quantitative; absolute determination of activity per unit volume of tissue⁶⁰ 	<ul style="list-style-type: none"> Not widely used for monitoring with radium-223⁵⁸ Lack of data leading to controversy about how results should be used: phase III trials to date used only bone scans¹⁵
CT	<ul style="list-style-type: none"> High level of anatomic detail¹⁵ 	<ul style="list-style-type: none"> Flare phenomenon⁴⁴
MRI <ul style="list-style-type: none"> Axial skeleton Whole-body 	<ul style="list-style-type: none"> Potential to detect metastasis early in bone growth, before gross bone remodeling is detected by bone scan/CT⁶⁰ Concurrent bone and node metastasis screening (whole body) 	<ul style="list-style-type: none"> Many centers still in feasibility stage of comparing whole-body MRI to established techniques⁶⁰ Added value over bone scan (eg, earlier and more reliable detection of metastasis) not yet proven⁴⁴
PET/CT novel tracers (Choline, PSMA, Fluciclovine)	<ul style="list-style-type: none"> Data suggest accurate detection of recurrence¹⁵ Concurrent bone and node metastasis screening 	<ul style="list-style-type: none"> Need validation with randomized prospective trials¹⁵ Added value over bone scan (eg, earlier and more reliable detection of metastasis) not yet proven¹⁵ Data on new tracers is lacking

Abbreviations: CT = computed tomography; ¹⁸F = ¹⁸F-fluoride; MRI = magnetic resonance imaging; NaF = sodium fluoride; PET = positron emission tomography; PSMA = prostate-specific membrane antigen; ^{99m}Tc = technetium-99m.

ongoing in patients with CRPC with bone metastases under radium-223 treatment, including measuring response (see [Supplemental Table 1](#) in the online version).

Disease monitoring in bone is problematic, with flare phenomena on computed tomography (CT) and bone scans reported.^{44,61} Whole body magnetic resonance imaging (MRI) and positron emission tomography imaging are considered to be the best options for assessing the extent of disease, whereas MRI appears to be most promising for measuring response,⁶² although this has not been validated for radium-223. However, MRI is not in regular clinical use owing to restricted resources. Imaging practice is, therefore, currently undergoing major changes in this setting.

Bone progression during radium-223 treatment has been shown to be rare.⁶¹ Frequent bone scintigraphy may therefore not be required, and unnecessary imaging should be avoided. A recent multicenter study retrospectively evaluated CT and bone scintigraphy response in 130 patients treated with radium-223.⁶¹ The authors concluded that bone progression was rare (6%), although a flare (pain and/or radiologic) phenomenon may be noted at 3 months and should not be confused with progression. CT imaging after 3 and 6 doses of radium-223 was suggested to rule out visceral disease progression that may necessitate discontinuing radium-223 in favor of chemotherapy or a new hormonal agent. CT scan data can also be used in patients with widespread bone metastases to screen for signs of potentially critical lesions in the spine, which should be further investigated with MRI.⁶³

Discussion on the timing for imaging while receiving radium-223 is summarized in Table 1. It was agreed that a bone and CT scan should always be performed before treatment with radium-223 and at 6 months to provide a new baseline after treatment. A CT scan at 3 months was recommended only if clinically indicated, to check for signs of progression (visceral disease). The majority also agreed, that if

available, a whole body MRI scan could be used to replace bone and CT scans. It was agreed that currently, in the absence of prospective data, imaging should only be performed to screen for visceral disease and suspected spinal cord compression, and not to evaluate response to radium-223.

When Should Radium-223 Be Stopped?

Discussion of when to stop radium-223 was held in the context of the recommendations from the Advanced Prostate Cancer Consensus Conference (APCCC). The APCCC general criteria for stopping a treatment recommends 2 out of the following 3 criteria: PSA progression, radiographic progression, and clinical progression.⁴⁴ In the event of unequivocal progression of soft tissue disease or development of visceral metastases without PSA progression or clinical deterioration, then treatment with radium-223 should be stopped and alternative therapy commenced. A biopsy taken to rule out second malignancy or small-cell histology should be considered. Men with mCRPC can often have worsening bone pain related to a nonmalignant process (degenerative disorders or osteoporotic fractures). Similarly, fatigue can be a side-effect of treatment and not a sign of disease progression.

As previously discussed, during the first course of radium-223, some patients may experience a flare phenomenon either as pain, a PSA rise, or a radiologic flare, all unrelated to disease progression. Thus, physicians should consider that only radiologic visceral progression as per CT scan (and suspected spinal cord compression) should be a clear indication for radium-223 treatment discontinuation.

In the absence of level 1 data, there was consensus that the APCCC stopping criteria were helpful and suitable for radium-223 treatment. However, as PSA is not a reliable marker, the importance of regular clinical assessment was emphasized.

Summary

Patients with mCRPC should ideally be discussed by a multi-disciplinary team, where the purpose of using radium-223 to prolong overall survival should be emphasized to both treating physicians and patients. It is important during treatment that the opportunity to administer as many of the available life-prolonging therapies is optimized. Radium-223 must be placed prior to the onset of visceral disease (lung, liver, or other organ metastases). Data from ongoing clinical studies may clarify the optimal placement of radium-223 in the current treatment paradigm. To date, there are no validated biomarkers for monitoring treatment on radium-223, and biomarker information would be best used in the context of other assessments to establish clinical progression. Repeated radiologic assessments are best avoided, and, unless otherwise indicated by clinical assessment, imaging is best used at the beginning and end of treatment to establish a baseline for further follow-up.

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Bayer, Janssen, Sanofi for Advisory Board participation. IvO reports advisory roles (compensated, institutional) for Astellas, Bayer, Janssen, Sanofi; Research support (institutional) from Janssen, Astellas; Travel support: Astellas. SN has received Honoraria from Bayer, Astellas, Ipsen, Sanofi-Genzyme, Novartis, Roche, Janssen for Advisory board participations and lectures.

Supplemental Data

Supplemental table accompanying this article can be found in the online version at <http://dx.doi.org/10.1016/j.clgc.2017.08.020>.

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Supplemental Table 1 Clinical Trials of Patients With mCRPC Treated With Radium-223 With Imaging as Primary Objectives

NCT Number (Study)	Estimated Enrollment	Imaging Technique	Outcome (Purpose)	Completion
NCT02429804 (phase I)	15	NaF/FDG/PET/MRI	Response	April 2018
NCT03011749	40	FLT/PET/CT	Uptake of FLT in hematologic bone marrow (as a marker of proliferative activity/toxicity)	January 2019
NCT02964988 (phase II)	43	uPAR PET/CT (tracer: ⁶⁸ Ga-NOTA-AE105)	uPAR PET/CT imaging (test applicability of method)	January 2019
NCT03062254 (phase II)	10	PET/CT (tracer ⁶⁸ Ga-HBED-CC-PSMA)	SUV-max (functional decline in intensity [uptake] as a surrogate for tumor cell killing)	July 2020
NCT02844647 (phase I)	10	MRI (¹³ Carbon hyperpolarized pyruvate)	Metabolic imaging (proof of concept study to image lactate, bicarbonate and pyruvate)	July 2018

Abbreviations: FGD = ¹⁸Flourine-fludeoxyglucose; FLT = ¹⁸Flourine-fluorothymidine; ⁶⁸Ga = ⁶⁸Gallium; HBED-CC = N,N' bis [2-hydroxy-5-(carboxyethyl)benzyl] ethylenediamine-N,N'-diacetic acid; MRI = magnetic resonance imaging; NaF = ¹⁸Flouride sodium fluoride; PET = positron emission tomography; PSMA = prostate-specific membrane antigen; uPAR = urokinase plasminogen activator.