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REVIEW

Sequencing of Radium-223 and Lutetium-177 Vipivotide Tetraxetan: Maximizing the Benefit of Systemic Targeted Radiation Therapy in Metastatic Castration-Resistant Prostate Cancer

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ABSTRACT

***Introduction*:** The goals of treatment for metastatic castration-resistant prostate cancer are disease management, improving quality of life, and prolonging life. Although androgen-receptor blockade and chemotherapy can control the disease for several years in most patients, resistance to treatment and continued disease progression are inevitable. Radionuclides have emerged as important tools in the therapeutic arsenal against prostate cancer. Appropriate sequencing with existing standards of care is paramount to ensure that patients get the maximum clinical benefit from as many life-prolonging therapies as possible during the treatment journey.

***Methods*:** We review radionuclide therapy for men with metastatic castration-resistant prostate cancer and present a treatment algorithm used in our specialist center to provide optimal care.

***Results*:** The goal of the treatment algorithm employed in our specialist center is to provide optimal patient care by using and sequencing appropriate systemic radionuclide therapy. The first step is to determine the extent of disease and metastases to offer personalized treatment to extend survival. Appropriate treatment sequencing can allow men to receive the life-prolonging benefits of radium-223 immediately upon bone-only progression, while remaining eligible to benefit from chemotherapy and/or lutetium-177 vipivotide tetraxetan (^{177}Lu-PSMA) upon further disease progression. Importantly, although prostate-specific antigen (PSA) is frequently perceived as a marker for prostatic disease burden, survival benefits of radionuclide therapy may be independent of change in PSA.

***Conclusions*:** As the majority of men with metastatic castration-resistant prostate cancer first present with bone-only metastases, they may be treated initially with radium-223, while still remaining eligible to benefit from chemotherapy and ^{177}Lu-PSMA upon subsequent progression of skeletal metastatic disease and/or the emergence of lymph node or visceral metastases. Graphical abstract available for this article.

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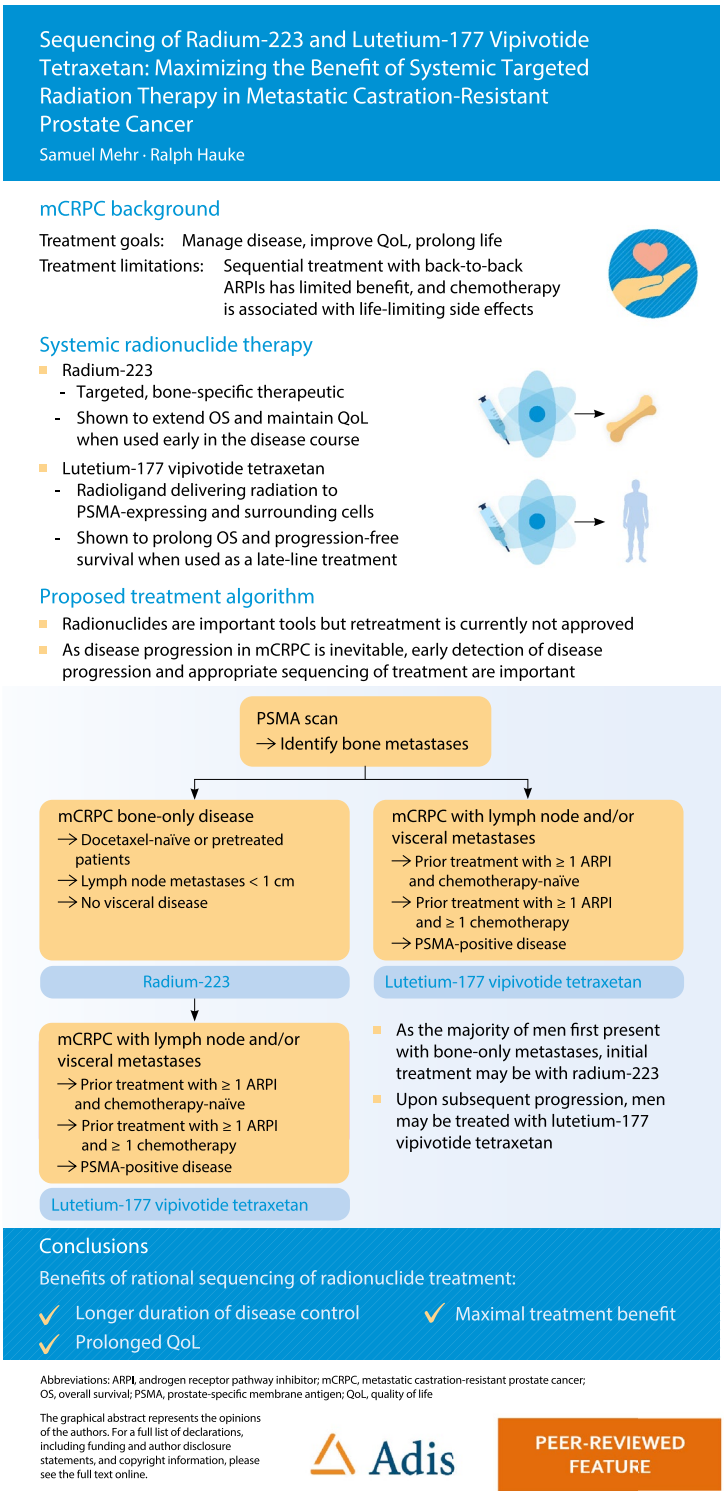
PLAIN LANGUAGE SUMMARY

This summary describes a narrative review on the treatment of men whose prostate cancer has spread beyond the prostate and no longer responds to hormonal therapy (metastatic castration-resistant prostate cancer). Such patients are often treated with intravenous radiopharmaceuticals, which target specific types of tumors or areas of the body. Two radiopharmaceuticals can be used to treat metastatic castration-resistant prostate cancer: radium-223 (Ra-223) and lutetium-177 vipivotide tetraxetan (Lu-177). Currently, each therapy is used once; thus, when the disease no longer responds to initial therapy, an alternative treatment is required. However, owing to the differences in their mechanism of action, Ra-223 and Lu-177 can be used sequentially to extend the duration of disease control. As prostate cancer initially spreads to bones only in 70% of patients, the authors suggest that patients eligible for treatment with radiopharmaceuticals should initially be treated with bone metastases-targeted Ra-223, reserving treatment with prostate-specific membrane antigen-targeted Lu-177 for more progressed disease (that has spread to the bones and/or lymph nodes or visceral organs). Using this approach will allow patients to achieve the longest duration of disease control, maximize treatment benefit, and prolong their quality of life.

Graphical Abstract:



Keywords: Radium-223; Lutetium-177 vipivotide tetraxetan; Metastatic castration-resistant prostate cancer; Bone metastases; Radionuclide therapy

Key Summary Points
Radionuclide therapies play an important role in the management of prostate cancer.
Appropriate sequencing of radionuclide treatments is paramount to deliver the maximum clinical benefit and prolonged disease control for men with metastatic castration-resistant prostate cancer (mCRPC).
As the majority of men with mCRPC first present with bone-only metastases, they may be treated initially with bone metastases-targeted radionuclide radium-223.
Upon subsequent progression of skeletal metastatic disease and/or the emergence of lymph node or visceral metastases, men with mCRPC may be treated with prostate-specific membrane antigen-targeting radionuclide lutetium-177 vipivotide tetraxetan.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.29881484.

INTRODUCTION

Castration-resistant prostate cancer (CRPC) is characterized by either biochemical and/or radiologic progression of prostate cancer in the setting of serum castration levels of testosterone [1]. It is estimated that 10–20% of men with prostate cancer develop CRPC within 5 years of initial diagnosis [2]. Moreover, ≥ 84% of men already have metastases at the time of CRPC diagnosis, and in those without metastases, 33% develop metastases within 2 years of diagnosis [2]. While the annual incidence of metastatic CRPC (mCRPC) has remained relatively stable, the prevalence of the disease has continued to increase, indicating that men are living longer with the disease [3].

More than 90% of distant metastases in prostate cancer occur in bone [4], and ~70% of men with metastatic disease are likely to have bone-only or bone-plus-lymph node metastatic disease [5]. Bone metastases are associated with skeletal events, which contribute to disability, reduced quality of life (QoL), increased mortality, and, for some men, long-term opioid use [6].

mCRPC is not curable; the goals of treatment are disease management, improving QoL, and prolonging life. Critical to these goals is a reduction in the total body tumor burden. Androgen receptor pathway inhibitors (ARPIs) or chemotherapy with a taxane are recommended as first-line treatments for mCRPC [7]. In routine practice, however, many men with mCRPC do not receive guideline-recommended treatments [8]. In addition, tumor cells eventually adapt to grow despite low androgen levels, rendering ARPIs ineffective [9]. Radium-223 dichloride (radium-223) is recommended in men with mCRPC, including those unfit for chemotherapy treatments or with symptomatic bone-only metastases [7]. Lutetium-177 vipivotide tetraxetan (^{177}Lu-PSMA) is recommended as useful in certain circumstances in men with mCRPC and prostate-specific membrane antigen (PSMA)-positive metastatic disease after an ARPI and docetaxel, or after an ARPI and docetaxel-naïve [10, 11].

Here we review radionuclide therapy for men with mCRPC that is no longer responsive to ARPIs and present an algorithm used in our specialist center to provide optimal care for men with this life-limiting disease.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

SYSTEMIC RADIONUCLIDE THERAPY FOR MCRPC

Patient Treatment Journey

Achieving optimal outcomes in mCRPC depends on a holistic approach, requiring thoughtful selection, timing, and sequencing of available therapies. Treatment options for men with mCRPC typically involve ARPIs, chemotherapy, immunotherapy, and radiopharmaceuticals [10]. Treatment with orally administered ARPIs such as enzalutamide (phase 3 AFFIRM and PREVAIL trials [12, 13]) and abiraterone acetate (phase 3 COU-AA-301 and COU-AA-302 trials [14, 15]) has demonstrated improved overall survival (OS) and delayed disease progression in mCRPC. However, resistance to ARPIs is developed by tumor cells over time, and sequential treatment with back-to-back ARPIs has limited benefit [16]. For patients whose tumors harbor specific homologous recombination repair gene mutations (most commonly BRCA1/2), poly (ADP-ribose) polymerase (PARP) inhibitors such as olaparib and rucaparib may be used, with evidence for improved radiographic progression-free survival (PFS) and OS (phase 3 PROfound and TRITON-3 trials, respectively [17, 18]).

Chemotherapy can improve OS in patients with mCRPC—most notably shown with docetaxel (phase 3 TAX 327 and SWOG 9916 trials) [19, 20]. Following progression after docetaxel, cabazitaxel is a next-generation taxane that has demonstrated improvement in OS in docetaxel-refractory mCRPC (phase 3 TROPIC trial) [21]. Treatment with such chemotherapeutic agents, however, can have undesirable and lifestyle-limiting side effects for some men [22].

Immunotherapies for mCRPC include the autologous cellular immunotherapy sipuleucel-T, which is usually considered before extensive ARPI or chemotherapy in patients with asymptomatic or minimally symptomatic mCRPC (phase 3 IMPACT trial) [23]. In addition, the immune checkpoint inhibitor pembrolizumab is used for mCRPC with high microsatellite instability or mismatch repair deficiency (phase 2 KEYNOTE trials) [24].

A potential alternative to consider is radionuclide therapy.

Radium-223

Radium-223 is a bone metastases-targeted radiopharmaceutical approved by the Food and Drug Administration in 2013 for treatment of symptomatic mCRPC without visceral disease [25]. Radium-223 decays through α-emission, resulting in predominantly irreparable double-stranded DNA breaks in tumor cells and the microenvironment in bone leading to cell death [25]. As the range of α-particles is < 100 µm, damage to surrounding tissue is minimized [26].

In the phase 3 ALSYMPCA study, 921 men with symptomatic mCRPC with two or more bone metastases, lymph node metastases < 3 cm, and no visceral disease received radium-223 every 4 weeks for six cycles, or placebo [27]. Radium-223 significantly improved OS versus placebo (14.9 months versus 11.3 months [hazard ratio {HR} 0.70; 95% confidence interval {CI} 0.58–0.83; $P < 0.001$]). Secondary outcomes were also improved with radium-223 versus placebo, including time to first symptomatic skeletal event, time to rise in alkaline phosphatase, prostate-specific antigen (PSA) progression, and QoL. Adverse events (AEs) were consistently less frequent among men receiving radium-223 [27], with fewer hospitalization days per patient than among those who received placebo (4.44 versus 6.68; $P = 0.004$) [28].

^{177}Lu-PSMA

^{177}Lu-PSMA combines the PSMA-targeting ligand vipivotide tetraxetan with lutetium-177 and was approved by the Food and Drug Administration in 2022 for PSMA-positive mCRPC previously treated with ARPIs and taxane-based chemotherapy [11]. ^{177}Lu-PSMA decays through β-emission, delivering radiation to PSMA-expressing and surrounding cells, inducing DNA damage and cell death [11]. β-particles are less likely to generate a lethal double-strand break than α-particles [29].

In the phase 3 VISION study, 831 men with PSMA-positive mCRPC previously treated with

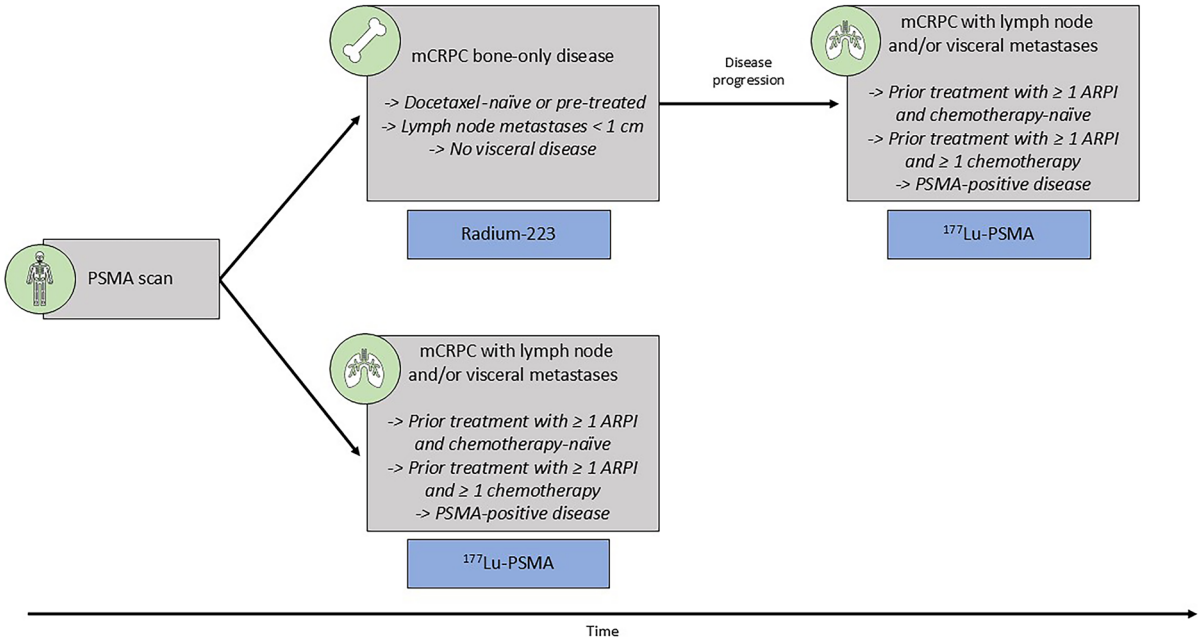


Fig. 1 Treatment sequencing of radium-223 and ^{177}Lu-PSMA for the treatment of mCRPC. *ARPI* androgen receptor pathway inhibitor, *^{177}Lu-PSMA* lutetium-177 vipivotide tetraxetan, *mCRPC* metastatic castration-resistant prostate cancer, *PSMA* prostate-specific membrane antigen

ARPIs and taxane-based chemotherapy were enrolled to receive standard of care (not including cytotoxic chemotherapy, radium-223, or investigational agents) with or without ^{177}Lu-PSMA [30]. ^{177}Lu-PSMA significantly prolonged radiographic PFS (8.7 months versus 3.4 months [HR 0.40; 99.2% CI 0.29–0.57; $P<0.001$]) and OS (15.3 months versus 11.3 months [HR 0.62; 95% CI 0.52–0.74; $P<0.001$]) versus standard of care alone. ^{177}Lu-PSMA also improved secondary outcomes, including objective response, disease control, and time to symptomatic skeletal

Table 1 Summary of patient characteristics for treatment with radium-223 or ^{177}Lu-PSMA (^{177}Lu-PSMA US Prescribing Information, 2025; Radium-223 US Prescribing Information, 2013)

Men who can receive radium-223 treatment	**Men unsuitable for radium-223 treatment**
Bone-only mCRPC	Lymph node metastases > 1 cm
Docetaxel-naïve or docetaxel pretreated	Visceral disease
Men who can receive ^{177}Lu-PSMA treatment	**Men unsuitable for ^{177}Lu-PSMA treatment**
PSMA-positive mCRPC	Extensive metastatic disease
Previously treated with ≥ 1 ARPI and considered appropriate to delay taxane-based chemotherapy	
Previously treated with ≥ 1 ARPI and ≥ 1 taxane-based chemotherapy	

ARPI androgen receptor pathway inhibitor, *^{177}Lu-PSMA* lutetium-177 vipivotide tetraxetan, *mCRPC* metastatic castration-resistant prostate cancer, *PSMA* prostate-specific membrane antigen

events. The incidence of AEs of grade 3+ was higher with ^{177}Lu-PSMA than with standard of care alone; however, QoL was not adversely affected in either arm.

In the phase 3 PSMAfore study in taxane-naïve patients with progressive PSMA-positive mCRPC, ^{177}Lu-PSMA prolonged radiographic PFS versus the ARPI change group (9.3 months versus 5.6 months [primary analysis: HR 0.41; 95% CI 0.29–0.56; $P<0.0001$]) [31]. In addition, prolonged time to worsening in self-reported health-related QoL and pain, and delayed time to first symptomatic skeletal event, were observed with ^{177}Lu-PSMA versus ARPI change [32].

Sequencing Therapy to Prolong Life in Men with mCRPC

Radium-223, chemotherapy, and ^{177}Lu-PSMA are life-prolonging therapies with different mechanisms of action that can be given in sequence [11, 25]. Retreatment is not approved with either radionuclide, so each can be used once in the treatment journey. It is therefore essential to use treatments such that patients may benefit from as many life-prolonging therapies as possible to achieve the longest possible disease control. As bone is the primary and principal site of disease progression for most men with mCRPC, treatment specifically targeting such sites represents a rational first-line approach.

Radium-223 can extend OS and maintain QoL when used early in the disease. Protocols for administering and managing men with radium-223 are well known and understood [33], and treatment can be administered by a urologist or medical oncologist on an outpatient basis without the need for referral to a specialist center. Patients who receive radium-223 need not avoid contact with other people immediately after treatment [25]. This approach can avoid delays in initiating treatment for bone metastases and slow further disease progression. Radium-223 is also effective and well tolerated regardless of chemotherapy exposure. This was demonstrated in the global, prospective REASSURE study [34] and in a subgroup analysis where the survival benefit was maintained regardless of prior docetaxel exposure [35]. A study assessing docetaxel with or without radium-223 is ongoing (DORA; NCT03574571). Additionally, radium-223 can be given first line in combination with enzalutamide in men with mCRPC with bone metastases. The efficacy of this approach has recently been confirmed in the global, randomized, phase 3 PEACE-3 study

Table 2 Radiation safety precautions for men with prostate cancer treated with radium-223 or ^{177}Lu-PSMA (^{177}Lu-PSMA US Prescribing Information, 2025; Radium-223 US Prescribing Information, 2013)

Radium-223 radiation protection precautions	^{177}Lu-PSMA radiation protection precautions
Stay well hydrated	Increase oral fluid intake
Flush the toilet several times after use	Urinate as often as possible
Wear gloves and wash hands when handling fluids such as urine, feces, or vomit	Limit close contact (≤ 3 feet) with household contacts for 2 days and with children and pregnant women for 7 days Do not have sexual intercourse for 7 days
Follow good hygiene practices to minimize radiation exposure to household contacts and caregivers	Use effective contraception during treatment and 14 weeks after the last dose
Use a condom and effective female contraception during sexual intercourse	Sleep in a separate bedroom from household contacts for 3 days, from children for 7 days, or from pregnant women for 15 days

^{177}*Lu-PSMA* lutetium-177 vipivotide tetraxetan

Table 3 Most common AEs (≥ 10% in clinical trial experience) for men with prostate cancer treated with radium-223 or ^{177}Lu-PSMA (^{177}Lu-PSMA US Prescribing Information, 2025; Radium-223 US Prescribing Information, 2013)

Radium-223 treatment AEs	^{177}Lu-PSMA treatment AEs
Nausea	Fatigue
Diarrhea	Dry mouth
Vomiting	Nausea
Peripheral edema	Anemia
Anemia	Decreased appetite
Lymphocytopenia	Constipation
Leukopenia	Vomiting
Thrombocytopenia	Diarrhea
Neutropenia	Thrombocytopenia
	Urinary tract infection
	Weight decrease
	Abdominal pain
	Peripheral edema

AE adverse event, *^{177}Lu-PSMA* lutetium-177 vipivotide tetraxetan

in which the addition of six cycles of radium-223 to enzalutamide 160 mg once daily significantly improved both radiographic PFS (HR 0.69; 95% CI 0.54–0.87; $P=0.0009$) and OS (HR 0.69; 95% CI 0.52–0.90; $P=0.0031$) versus enzalutamide alone [36].

As treatment with ^{177}Lu-PSMA prolonged OS and PFS in mCRPC refractory to ARPIs and taxane chemotherapy in the VISION study [30], its indication, until recently, required previous chemotherapy [11]. A small, open-label, noninferiority study demonstrated that ^{177}Lu-PSMA was safe in chemotherapy-naïve patients with mCRPC [37], and interim results from the ongoing phase 3 PSMAfore study (NCT04689828) have led to the expansion of the indication to patients who are considered appropriate to delay taxane-based chemotherapy [11, 31, 32]. Therefore, ^{177}Lu-PSMA can be considered as an effective treatment alternative after progression on a previous ARPI. An open-label, randomized, phase 3 study is ongoing to evaluate the efficacy and safety of ^{177}Lu-PSMA-617 in combination with standard of care, versus standard of care alone, in adult male patients with PSMA-positive mCRPC (NCT04720157). The infrastructure, staffing level, expertise, and workflow necessary for ^{177}Lu-PSMA require that it be administered at specialist centers, which could delay treatment [33]. For example, training may be required for the use of nuclear medicine tracers and obtaining theragnostic compounds, additional radiation safety precautions and rooms are required for the β-emitting therapy, and additional staff may be required to oversee the more complex supply chain.

As progression in mCRPC is inevitable, treatment sequencing can allow men to receive the life-prolonging benefits of radium-223 immediately upon bone-only progression under the care of their urologist or medical oncologist, while remaining eligible to receive subsequent chemotherapy, if appropriate, and ^{177}Lu-PSMA upon further progression. If bone-only metastases are treated early with ^{177}Lu-PSMA, options become limited when the disease inevitably spreads to soft tissue. We therefore recommend that radium-223 and ^{177}Lu-PSMA be used sequentially, with radium-223 initiated first for bone-only progression. Several studies have investigated radium-223 given before ^{177}Lu-PSMA and support this approach. In the VISION study, 17.4% of patients had received radium-223 before ^{177}Lu-PSMA without adversely affecting efficacy, and with positive OS and radiographic PFS outcomes [30]. Retrospective studies have also shown that using radium-223 before ^{177}Lu-PSMA is feasible with acceptable safety [38, 39], and that initiation of ^{177}Lu-PSMA ≤ 8 weeks after radium-223 in men with progressive bone-metastatic disease is feasible and effective [40]. The RALU study demonstrated that treating men with ^{177}Lu-PSMA ≤ 6 months after completing radium-223 was feasible and well tolerated [41]. There are no data on sequential treatment with ^{177}Lu-PSMA before radium-223. TREATMENT ALGORITHM.

Determining Treatment Eligibility

The goal of the algorithm employed in our specialist center is to provide optimal care by

Table 4 AEs for men with prostate cancer treated with radium-223 or ^{177}Lu-PSMA and associated management strategies (^{177}Lu-PSMA US Prescribing Information, 2025; Radium-223 US Prescribing Information, 2013)

AE with radium-223 treatment	Management strategy
Dehydration (may occur as a result of diarrhea, nausea, and vomiting)	Monitor patients' oral intake and fluid status Promptly treat patients displaying signs of dehydration or hypovolemia
Bone marrow suppression	Monitor patients closely and provide supportive care measures where necessary Permanently discontinue treatment in patients experiencing life-threatening complications
AE with ^{177}Lu-PSMA treatment	**Management strategy**
Myelosuppression (including anemia, thrombocytopenia, leukopenia, and neutropenia)	Perform complete blood counts before and during treatment Grade 2: withhold treatment until improvement Grade ≥ 3: withhold treatment until improvement or reduce dose by 20% Recurrent grade ≥ 3: permanently discontinue treatment
Renal toxicity (including acute kidney injury and increased creatinine)	Advise patients to remain well hydrated and to urinate frequently Perform kidney function laboratory tests, including serum creatinine and calculated creatinine clearance, before and during treatment Grade ≥ 2: withhold treatment until improvement or reduce dose by 20% Grade ≥ 3 or recurrent renal toxicity after dose reduction: permanently discontinue treatment
Dry mouth	Grade 2: withhold treatment until improvement and consider reducing treatment by 20% Grade 3: withhold treatment until improvement or reduce dose by 20% Recurrent grade 3: permanently discontinue treatment
Gastrointestinal toxicity	Grade ≥ 3: withhold treatment until improvement or reduce dose by 20% Recurrent grade ≥ 3: permanently discontinue treatment
Fatigue	Grade ≥ 3: withhold treatment until improvement
Electrolyte/metabolic abnormalities	Grade ≥ 2: withhold treatment until improvement
AST or ALT elevation	≥ 5 × ULN: permanently discontinue treatment

AE adverse event, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *^{177}Lu-PSMA* lutetium-177 vipivotide tetraxetan, *ULN* upper limit of normal

appropriately sequencing systemic radionuclide therapy (Fig. 1). Once the diagnosis is confirmed, it is important to determine the extent of the disease and metastases to offer personalized life-prolonging treatment. The first step of the algorithm is therefore a PSMA positron emission tomography (PET) scan to identify bone metastases. Conventional imaging, such as computed tomography (CT), magnetic resonance imaging, and bone scintigraphy, face significant limitations, including insufficient sensitivity to characterize some bone metastases [42]. PSMA PET scans can be used to identify additional men with bone-only disease who may be eligible for radium-223 treatment. Although very rare, it should be noted that PSMA scans can detect nonmalignant or nonprostatic diseases [43]. For example, in active sarcoidosis, apparent PSMA expression can be seen in hilar and mediastinal lymph nodes on PET/CT scans. As the radium-223 label does not mention lymph node involvement, this can be confusing for physicians. Criteria from the ALSYMPCA study excluded treatment with radium-223 for men with lymph node metastases > 3 cm [27].

^{177}Lu-PSMA treatment is the most effective in men with a high level of PSMA expression, so PSMA-positive status is determined with gallium-68-labeled PSMA-11 PET/CT [30]. Criteria from the VISION study excluded men with PSMA-negative lesions, defined as PSMA uptake equal to or lower than that of liver parenchyma in any lymph node ≤ 2.5 cm, in any metastatic solid-organ lesions ≤ 1.0 cm, or in any metastatic bone lesion with a soft tissue component ≤ 1.0 cm [30].

Treatment with Radium-223 and ^{177}Lu-PSMA

Once disease extent is assessed, treatment eligibility can be determined. Criteria for radium-223 treatment include: docetaxel-naïve or docetaxel pretreated; bone-dominant disease (without or with limited lymph node disease as outlined above); and absence of visceral disease (Table 1). Men with disease progression after radium-223 can be considered for ^{177}Lu-PSMA. Criteria for ^{177}Lu-PSMA treatment include: prior treatment with one or more ARPIs and one or more chemotherapy agents; PSMA-positive disease; and possible visceral disease (Table 1).

It is logical to wait for bone marrow recovery before administering ^{177}Lu-PSMA upon disease progression. In the RALU study, ^{177}Lu-PSMA treatment within 6 months of completing radium-223 was feasible and well tolerated [41]. In addition, OS was similar with ^{177}Lu-PSMA < 6 months versus > 6 months after completing radium-223. The AlphaBet study is assessing the radionuclides radium-223 and ^{177}Lu-PSMA in combination (NCT05383079).

Practical Aspects of Treating Men with Radium-223 and ^{177}Lu-PSMA

Public perception of radioactivity and the complexity of radiopharmaceutical treatment may be a challenge when treating mCRPC. There are numerous precautions that men must implement during and after treatment to limit radiation exposure to caregivers and family. This is particularly important for ^{177}Lu-PSMA because penetrative β-therapy requires more rigorous procedures (Table 2).

Initiation of ^{177}Lu-PSMA may be slow owing to there being waiting lists for referral to the few centers approved to deliver treatment. Furthermore, the requirement for taxane pretreatment can cause delays if insurers' permissions must be obtained before initiation.

Men should be monitored regularly for AEs to adjust dosing or delay or discontinue treatment (Tables 3 and 4).

Monitoring PSA

As men with healthy prostates have minimally detectable blood PSA levels, PSA is frequently perceived as a marker for prostatic disease burden, with a low level regarded as an indicator of treatment effect. However, PSA is not always a reliable predictor of disease state or treatment outcomes, particularly in advanced disease.

Specifically, PSA levels are not a reliable marker for radium-223 treatment response, as radium-223 does not target the androgen receptor pathway and so does not impact PSA gene expression [44]. After radium-223

treatment, there is often no change or even an increase in PSA levels, despite beneficial outcomes including prolonged survival. In the ALSYMPCA study, only 16% of men achieved a ≥ 30% reduction in PSA with radium-223; however, lack of PSA reduction did not impact survival outcomes, with a 30% reduction in risk of death versus placebo [27]. In addition, a retrospective study in 160 men with mCRPC treated with radium-223 determined that a PSA flare does not necessarily indicate a lack of response [45]. In the real-world ROTOR registry of men treated with radium-223 ($N = 305$, 66% pretreated with taxanes and/or abiraterone or enzalutamide), median OS was similar to that of the treatment arm of ALSYMPCA (15.2 versus 14.9 months, respectively), and PSA response remained uncommon (5.3% of men achieved a PSA decrease ≥ 30%) [46]. It has been hypothesized that PSA increases may correspond to a high degree of tumor cell death, as PSA is released through tumor cell lysis [45]; other possible explanations relate to cellular heterogeneity and diversity in advanced disease states [47].

After ^{177}Lu-PSMA treatment there is often a decrease in PSA. In the VISION study, PSA decline was thought to predict outcomes during treatment with ^{177}Lu-PSMA, as greater PSA decline was associated with prolonged radiographic PFS and OS [48]. It should also be noted that some active visceral metastases do not produce PSA [49].

Overall, radium-223 and ^{177}Lu-PSMA improve OS despite differential effects on PSA. With the rise of direct-to-consumer healthcare marketing and men becoming more involved in treatment decisions, it is important for physicians to discuss why sequential treatment may be beneficial regardless of PSA change to maximize treatment options and duration of disease control. At our US expert center, it is common for urologists to refer men with mCRPC for "systemic targeted radiation therapy," allowing a decision on the preferred approach to be made following a detailed discussion with the specialist physician.

DISCUSSION

Sequencing of radionuclide treatment is paramount to maximize options and clinical benefit. Most men with mCRPC present with bone-only metastases; as such, a rational approach is to treat initially with radium-223, preserving eligibility for chemotherapy and ^{177}Lu-PSMA upon disease progression.

A study investigating the safety of radium-223 and ^{177}Lu-PSMA in combination is estimated to be complete in 2026 (AlphaBet; NCT05383079). This open-label study will enroll 36 men with mCRPC who progressed on second-generation androgen receptor antagonists to evaluate the maximum tolerated dose, dose-limiting toxicities, recommended phase 2 dose, and PSA response rate of radium-223 plus ^{177}Lu-PSMA.

Importantly, although radium-223 can be administered by nuclear medicine departments available to most urologists and medical oncologists, ^{177}Lu-PSMA must be given in specialist centers, affecting the ability of smaller or more rural practices to offer treatment. The high upfront cost associated with programs enabling men to receive ^{177}Lu-PSMA could be a barrier to the proposed algorithm; however, it is important to advocate for patient accessibility, and these programs can be cost-effective once established [33].

CONCLUSION

It is critical that effective treatments for men with mCRPC are not delayed. Appropriate treatment sequencing is paramount to allow patients to benefit from as many life-prolonging therapies as possible and to achieve the longest duration of disease control. Because most men with mCRPC present with bone-only metastases, if they are considered for radioligand therapy, they should be treated initially with radium-223, reserving ^{177}Lu-PSMA treatment for progression of skeletal metastatic disease and/or emergence of lymph node or visceral metastases.

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Declarations

Conflict of Interest. Samuel Mehrreports payments for professional services from Cellectar Biosciences, Novartis, Bayer, Blue Earth Therapeutics, RayzeBio, Perspective Therapeutics, Spectrum Pharmaceuticals and Siemens Healthineers. Ralph Hauke reports payment for expert testimony from TeleDoc; leadership or fiduciary roles with ASCO, Midwest Private Practice Associates ACO, and the Nebraska Oncology Society; and having served on advisory committees to AstraZeneca.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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