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# Radium-223 Within the Evolving Treatment Options for Metastatic Castration-resistant Prostate Cancer: Recommendations from a European Expert Working Group

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**Abstract**

Several ongoing clinical trials are investigating novel therapies and combinations of existing therapies for the treatment of patients with metastatic castration-resistant prostate cancer. One such trial, ERA 223, has shown that the combination of abiraterone plus radium-223 did not improve symptomatic skeletal event-free survival compared with abiraterone plus placebo. Furthermore, an increase in bone fractures was observed with the combination of abiraterone and radium-223 in the study, particularly in patients not receiving bone health agents (denosumab or zoledronic acid). The results led to a change in the indication of radium-223 in Europe and also highlighted a need for greater awareness of bone health in patients with prostate cancer. Following a meeting to discuss these issues, we report in this article our views on the role of radium-223 within the emerging treatment options for patients with metastatic castration-resistant prostate cancer. We discuss best practices, and provide expert recommendations for preserving bone health and sequencing of life-prolonging therapies in patients with prostate cancer in order to achieve optimal outcomes.

***Patient summary:*** We provide recommendations on maintaining bone health, sequencing of treatments, and the role of radium-223 therapy in prostate cancer. Radium-223 is a valuable treatment option for patients with castration-resistant prostate cancer and bone metastases. Monitoring and maintaining bone health are essential for patients with prostate cancer, and should be considered at the initiation of androgen deprivation therapy.



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## 1. Introduction

Patients with metastatic prostate cancer, and those with recurrence following surgery, typically receive androgen deprivation therapy (ADT) as the first-line systemic treatment, increasingly in combination with abiraterone [1,2], six cycles of docetaxel [3,4], or even local radiation therapy for newly diagnosed patients with low-volume metastatic disease [5].

Approved therapies that prolong overall survival or metastasis-free survival for patients with castration-resistant prostate cancer (CRPC) include abiraterone [6], enzalutamide [7,8], apalutamide [9], docetaxel [10], cabazitaxel [11], and radium-223 [12]. In addition, denosumab and zoledronic acid (bone health agents [BHAs]) are approved for the prevention of skeletal-related events (SREs) [13,14]. Following the introduction of these therapies, patients can often now live for longer than 3 yr after the diagnosis of metastatic CRPC (mCRPC) [15,16]. However, the optimal sequence of these agents is unclear, and patients will ultimately progress following initial response to these therapies. Therefore, there are ongoing efforts to investigate novel treatments and rational combinations of existing therapies.

The ERA 223 trial investigated the combination of abiraterone and prednisolone with radium-223. The study did not meet its primary endpoint of symptomatic skeletal event-free survival (SSE-FS), and an increase in bone fractures was observed with the combination of abiraterone and prednisolone plus radium-223, most notably in patients not receiving BHAs [17]. The results of this trial led to a change in the indication of radium-223 in the European Union (EU) [18] but have also highlighted a need for increased vigilance of bone health in patients with prostate cancer.

This article reports on the views of a group of urologists, medical oncologists, and radiation oncologists from Europe experienced in treating patients with advanced prostate cancer who met to discuss these topics. We provide an overview of the use of radium-223 in the emerging treatment landscape for mCRPC, and discuss best practices for preserving bone health and sequencing therapies based on our clinical experience.

## 2. Radium-223

Radium-223 mimics calcium and binds to hydroxyapatite in newly formed bone. After intravenous administration, it is taken up into areas of increased bone turnover, such as bone metastases, where it decays to emit predominantly high-energy, short-range alpha particles [19]. These alpha particles induce double-stranded DNA breaks in prostate cancer cells, osteoblasts, and osteoclasts within bone metastases, resulting in a localised cytotoxic effect [20]. In mouse prostate cancer models, radium-223 was preferentially deposited in intratumoural bone matrix and inhibited tumour-induced bone formation, highlighting its ability to inhibit osteoblast proliferation [20].

The pivotal phase 3 ALSYMPCA trial enrolled patients with CRPC and symptomatic bone metastases who had received prior docetaxel, or were not healthy enough or declined to receive it. Patients were randomised to receive radium-223 or placebo. Radium-223 significantly improved overall survival compared with placebo (median 14.9 vs 11.3 mo [hazard ratio {HR} 0.70, 95% confidence interval {CI} 0.58–0.83; $p < 0.001$]). Furthermore, time to symptomatic skeletal events (SSEs) was significantly delayed with radium-223 compared with placebo (median 15.6 vs 9.8 mo [HR 0.66, 95% CI 0.52–0.83; $p < 0.001$]). There were no clinically meaningful differences in the frequency of grade 3 or 4 haematological adverse events between the treatment groups [12]. Radium-223 remained well tolerated with a low incidence of myelosuppression at long-term follow-up [21]. Radium-223 also improved health-related quality of life, with significantly more patients having meaningful improvements in Functional Assessment of Cancer Therapy-Prostate (25% vs 16%; $p = 0.02$) and EuroQoL-5 dimensions (29% vs 19%; $p = 0.004$) scores in the radium-223 group compared with the placebo group [22]. Based on ALSYMPCA, radium-223 was approved for the treatment of patients with mCRPC and symptomatic bone metastases. Radium-223 also earned the highest score possible on the European Society for Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale, a validated and reproducible tool that assesses the magnitude of benefit of anticancer therapies taking into account their efficacy and safety [23].

## 3. Combining abiraterone and prednisolone with radium-223: implications of the ERA 223 trial

Abiraterone is a CYP17A1 inhibitor that acts in prostate cancer cells, the testes, and adrenal glands to prevent biosynthesis of androgen [24]. This mechanism of action was thought to be potentially complementary to that of radium-223. Furthermore, abiraterone and radium-223 originally appeared to have nonoverlapping safety profiles. For these reasons and in the absence of prospective, randomised clinical trial data, these two agents were often combined in clinical practice, either concurrently or by adding radium-223 to ongoing abiraterone therapy at the point of prostate-specific antigen (PSA) progression (termed "layering"). Furthermore, over one-quarter of patients in an international early-access, open-label, single-arm phase 3b study of radium-223 received concomitant abiraterone or enzalutamide. For patients who received radium-223 in combination with abiraterone, more than one-half were already receiving ongoing abiraterone treatment prior to the first injection of radium-223 [25]. A post hoc analysis showed that overall survival was longer for patients who received radium-223 in combination with either abiraterone or enzalutamide than those who received radium-223 alone [25]. These data highlighted the need to evaluate the combination of abiraterone and radium-223 in a prospective, randomised study.

ERA 223 (NCT02043678) is a randomised phase 3 trial that investigated abiraterone and prednisolone plus radium-223 versus abiraterone and prednisolone plus placebo in asymptomatic or mildly symptomatic

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abiraterone- and chemotherapy-naïve patients with mCRPC. The primary endpoint was SSE-FS, defined as the time from randomisation to the first SSE or death from any cause. SSEs were defined as new symptomatic pathological bone fractures, spinal cord compression, use of external beam radiotherapy for skeletal symptoms, or tumour-related surgical intervention [17].

In November 2017, the study was unblinded prematurely at the Independent Data Monitoring Committee's recommendation because of the observation that more fractures and deaths had occurred in the abiraterone plus radium-223 group than in the control group at an unplanned analysis. All patients had already completed study-specified radium-223/placebo treatment prior to unblinding. The study was amended to allow initiation of BHAs, and treatment was continued as per protocol [17].

At the primary analysis of the study, SSE-FS was not significantly different for abiraterone plus radium-223 versus abiraterone plus placebo (median 22.3 vs 26.0 mo [HR 1.122, 95% CI 0.917–1.374; $p = 0.2636$]). The secondary endpoint of overall survival was also not significantly different between treatment groups (median 30.7 vs 33.3 mo [HR 1.195, 95% CI 0.950–1.505; $p = 0.1280$]). The overall incidence of adverse events was similar between treatment groups. However, bone fractures were much more common with the combination of abiraterone plus radium-223 (29% vs 11%). Among patients with fractures and imaging scans reviewed centrally (80 in the combination group and 27 in the control group), the higher fracture incidence in the combination group was largely driven by osteoporotic fractures [17].

Based on the results of ERA 223, the combination of radium-223 and abiraterone is now contraindicated in the EU, and the combination of radium-223 with other systemic cancer therapies (except for luteinising hormone-releasing hormone [LHRH] analogues) is not recommended [18]. However, several ongoing trials are investigating the combination of radium-223 with other systemic anticancer therapies, including randomised phase 3 trials of radium-223 in combination with docetaxel (NCT03574571, DORA) and in combination with enzalutamide (NCT02194842, PEACE III). Following the ERA 223 results, BHA use is now mandatory in the PEACE III trial and patients can initiate radium-223 up to 8 wk after starting enzalutamide, rather than concurrently. It has been hypothesised that this approach may be more effective than concurrent treatment [26].

## 4. Recommendations on bone health in men with prostate cancer

Most patients with prostate cancer exhibit some degree of osteopenia. ADT results in increased bone turnover and decreased bone mineral density (termed "cancer treatment-induced bone loss"), further increasing the risk of osteoporosis and osteoporotic fractures [27]. Notably, other systemic therapies for prostate cancer, such as glucocorticoids [28] and the antihormonal agents abiraterone, enzalutamide, and apalutamide [29–31], are also associated with increased fracture risk (Fig. 1) due to various potential mechanisms. For example, prednisolone and other glucocorticoids lead to bone density loss in a dose- and duration-dependent manner [28,32], whereas abiraterone inhibits the production of testosterone, known to play a role in preventing bone loss [33]. Enzalutamide and apalutamide inhibit the androgen receptor, potentially blocking the bone-protective effects of androgens, and are associated with adverse effects related to the central nervous system that may lead to falls and subsequent traumatic fractures [7–9].

Enzalutamide, apalutamide, and darolutamide have been shown to significantly prolong metastasis-free survival when added to ADT in men with nonmetastatic CRPC (nmCRPC) [8,9,34], while abiraterone significantly improves overall survival when added to ADT in men with metastatic hormone-sensitive prostate cancer (mHSPC) [1,2]. Owing to these recent advances, new antihormonal therapies are now being utilised earlier in the treatment paradigm. Therefore, patients with prostate cancer are receiving more potent treatments and longer durations of intensified ADT, further increasing their risk of bone loss and fractures [27,35].

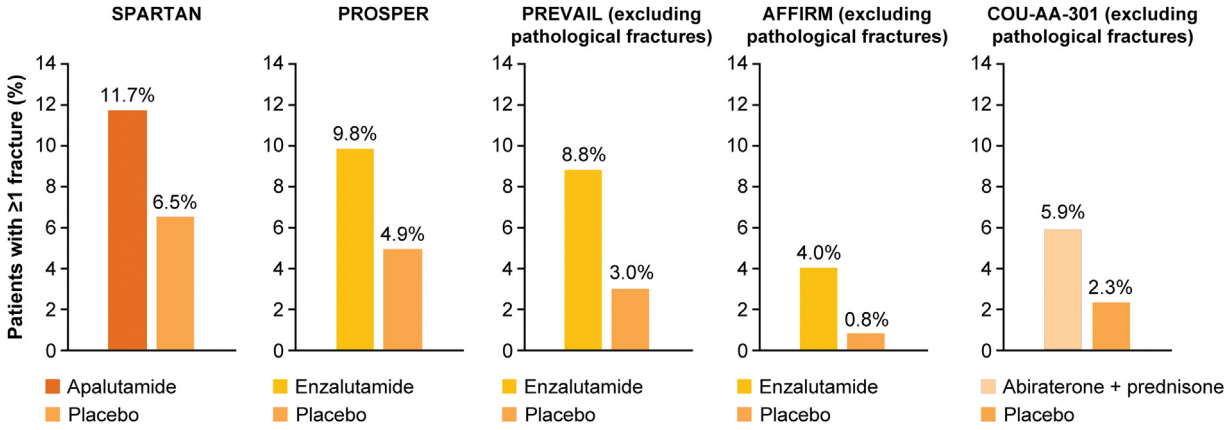


**Fig. 1 – Incidence of fractures in pivotal trials of antihormonal therapies. Incidence of fractures in the SPARTAN (apalutamide in nmCRPC) [9], PROSPER (enzalutamide in nmCRPC) [30], PREVAIL (enzalutamide in chemotherapy-naïve mCRPC) [30], AFFIRM (enzalutamide in mCRPC after docetaxel) [30], and COU-AA-301 (abiraterone plus prednisone in mCRPC after docetaxel) trials [29].**

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Bone metastases are common in patients with metastatic prostate cancer [36]. Bone metastases are highly osteoblastic due to signalling crosstalk between prostate cancer cells, osteoblasts, and osteoclasts. This leads to reciprocal stimulation of these cells, abnormal bone remodelling, and formation of fragile bone [37], which in turn puts patients with metastatic prostate cancer at risk of pathological bone fractures and other SREs [38]. SREs are associated with lower quality of life, increased treatment costs, and shorter overall survival [39–41].

Owing to the inherent risk of cancer treatment–induced bone loss and fractures from anticancer therapies and bone metastases, bone health should be evaluated regularly in patients with prostate cancer and use of BHAs to maintain bone health should be considered. In the ERA 223 trial, initiation of BHAs during study treatment was not allowed to avoid confounding effects on study outcomes. BHAs were permitted only for those patients who were receiving BHAs at baseline, who represented approximately 40% of the overall study population [17]. A post hoc analysis revealed baseline BHA use to be associated with a substantially lower fracture risk in both treatment groups. In the combination and control groups, fractures occurred, respectively, in 15% and 7% of patients with BHAs versus 37% and 15% of patients without BHAs [17]. These data reinforce the importance of using BHAs during treatment of mCRPC with radium-223 and antihormonal agents.

Data from real-world studies demonstrate that BHAs are underutilised in patients with mCRPC, with wide geographical variation [42,43], despite recommendations in clinical practice guidelines [44,45]. Only 50% of patients in a noninterventional observational study of radium-223 in routine clinical practice were receiving BHAs [43]. Common arguments against prescribing BHAs include the lack of demonstrated overall survival benefit and the fact that life-prolonging agents also delay SREs/SSEs (abiraterone [46], enzalutamide [47], radium-223 [12,48]), giving the impression that addition of BHAs would be superfluous. Furthermore, concerns over increased risk of osteonecrosis of the jaw, hypocalcaemia, and renal toxicity with longer BHA exposure, in addition to cost, may explain why some physicians seem reluctant to administer BHAs concurrently with systemic anticancer therapies in mCRPC. However, post hoc analyses from clinical trials of abiraterone and radium-223 have demonstrated the benefit in terms of efficacy for the combination of these agents with BHAs and similar safety profiles regardless of concomitant BHA use [25,49]. In addition, baseline zoledronic acid use in the prospective ALSYMPCA trial was associated with a lower risk of SSEs [48].

SRE-based endpoints do not incorporate nonpathological fractures, and data on the incidence of these fractures during systemic treatment for mCRPC are limited. However, it is likely that while a treatment may delay pathological fractures and other SREs, the subsequent increase in treatment duration will increase the risk of osteoporosis and osteoporotic fractures. Use of BHAs concomitantly with systemic anticancer treatments may help protect bone and mitigate this risk.

We strongly recommend evaluation of bone health and fracture risk prior to initiating ADT, and regular monitoring during treatment. Bone mineral density should be assessed using dual-energy X-ray scan before and during ADT. Of note, only one-quarter of physicians in a European survey assessed osteoporotic risk prior to initiating ADT [50]. Fracture risk should also be determined by the Fracture Risk Assessment Tool (FRAX) [51], which evaluates a patient's fracture risk through the use of clinical risk factors alone or in combination with bone mineral density; ADT is considered a cause of secondary osteoporosis when using the FRAX tool. Patients on ADT who are at risk of a fracture based on bone mineral density and FRAX score should receive BHAs as soon as possible (unless contraindicated) in order to strengthen bone and prevent osteoporosis. We also recommend advising patients on the benefits of weight-bearing exercise to strengthen bone, a measure stressed far too little in daily clinical practice.

Patients receiving ADT should be advised to take calcium and vitamin D supplements. BHAs should be initiated in patients with osteopenia to prevent or treat osteoporosis, for example, denosumab 60 mg every 6 mo and zoledronic acid 5 mg every year. For patients with bone metastases, BHAs should be initiated upon development of castration resistance, regardless of other systemic therapies, to prevent or delay SREs, for example, denosumab 120 mg every 4 wk and zoledronic acid 4 mg every 3 mo. Physicians choosing BHA therapy for any patient should also consider associated toxicity and take relevant steps to protect against it. For example, poor dentition should be resolved prior to initiating a BHA, and serum calcium levels and renal function should be monitored regularly. Of note, duration of BHA therapy for asymptomatic men with mCRPC and bone metastases in the absence of significant toxicity is still an area of debate [52].

## 5. Treatment sequencing in mCRPC

There are currently no data to inform the optimal sequencing of the life-prolonging therapies available for patients with mCRPC, and recommendations from clinical practice guidelines are limited. Abiraterone or enzalutamide is typically the most common first-line therapy used in real-life clinical practice [53]; however, patients will ultimately progress and require a change in therapy. Treatment sequencing in mCRPC remains a challenge for physicians [54]; this is further complicated by the evolution of the treatment landscape, and use of abiraterone and docetaxel in the mHSPC setting [1–4] and enzalutamide, apalutamide, and darolutamide in the nmCRPC setting [8,9,34].

Treatment choice and selection of systemic therapies should be based on a physician's best judgement, considering the needs and preferences of each patient. For example, some patients may suffer from pre-existing or treatment-related comorbidities, making them unsuitable for specific therapies. Other patients may wish not to opt for certain treatments due to practical or toxicity concerns. Therefore, there will be a subgroup of patients who are ineligible for or refuse certain treatments. In the PREVAIL trial of

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enzalutamide in men with chemotherapy-naïve mCRPC, 48% of patients received no systemic therapy after enzalutamide; only 41% of patients received docetaxel after enzalutamide [15]. In the COU-AA-302 trial of abiraterone in men with chemotherapy-naïve mCRPC, 48% of patients received docetaxel after abiraterone. A higher proportion of older patients received no subsequent systemic treatments, with 43% of patients over the age of 75 yr receiving no systemic therapy after abiraterone [55].

Several studies have been conducted to assess the optimal sequence of abiraterone and enzalutamide treatment in men with mCRPC. These studies clearly demonstrate that enzalutamide given sequentially to abiraterone, and vice versa, results in a very limited response to the second agent. In a phase 4 study, patients with chemotherapy-naïve mCRPC with an initial response to enzalutamide and subsequent PSA progression were randomised to receive abiraterone in combination with continued enzalutamide or abiraterone in combination with placebo. The median time to PSA progression (2.8 mo) was short and the PSA response rate (2%) was very low for patients who received abiraterone after enzalutamide [56]. In a randomised phase 2 crossover study, median time to PSA progression was 2.7 mo in patients receiving enzalutamide after abiraterone and 1.3 mo in patients receiving abiraterone after enzalutamide [57]. By way of comparison, median time to PSA progression in patients receiving first-line enzalutamide or abiraterone in phase 3 trials was 11.2 or 11.1 mo, respectively [6,7]. The lack of efficacy of sequential abiraterone and enzalutamide is thought to be due to common mechanisms of resistance, such as androgen receptor mutations and splice variants [58], suggesting that a therapy that acts via a different mechanism of action would be more effective than a sequential antihormonal agent.

Thus, current evidence suggests that back-to-back use of abiraterone and enzalutamide exposes the patient to an ineffective subsequent treatment with associated toxicity, and often wastes already limited healthcare resources. Therefore, we recommend that patients who have received abiraterone or enzalutamide for mCRPC be considered ineligible for immediate switch to another antihormonal therapy if other options are available due to the likelihood of lack of efficacy. We also consider that this may be true for patients receiving abiraterone for mHSPC and those receiving apalutamide or enzalutamide for nmCRPC. Data will be required to confirm this.

## 6. Radium-223 within the mCRPC treatment landscape

Abiraterone and enzalutamide were not available at the time of the phase 3 ALSYMPCA trial, and data for patients who received radium-223 after these agents are lacking. However, based on our clinical experience, radium-223 is a valuable treatment option for men with mCRPC and bone metastases, particularly following progression on first-line abiraterone or enzalutamide treatment. Preliminary real-world evidence for radium-223 has not revealed any new safety findings, with treatment-related adverse events occurring in 45% of patients who received radium-223 treatment after abiraterone or enzalutamide, compared with 37% of all radium-223-treated patients [59]. Median overall survival was 11 mo in patients who received radium-223 after abiraterone [42,43].

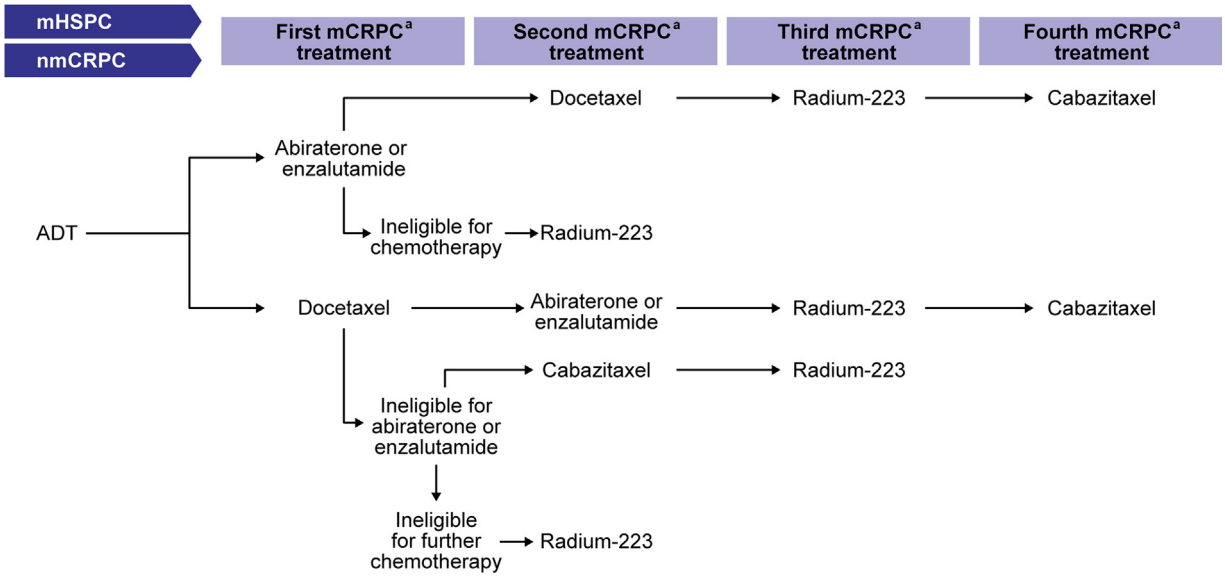


**Fig. 2 – Sequencing of systemic therapies for mCRPC. Potential sequencing options for approved life-prolonging agents following progression on ADT. These are illustrative algorithms based on the revised EU indication for radium-223. Not all potential treatment options are shown. Concurrent use of bone health agents to treat osteoporosis or for patients with bone metastases is recommended. Sequential use of abiraterone and enzalutamide (or vice versa) is not considered as an option due to likely futility of treatment. Consider clinical trials or best supportive care after all available systemic therapies have been administered. ADT = androgen deprivation therapy; EU = European Union; mCRPC = metastatic castration-resistant prostate cancer; mHSPC = metastatic hormone-sensitive prostate cancer; nmCRPC = nonmetastatic castration-resistant prostate cancer. [a] mCRPC with bone metastases and no visceral metastases.**

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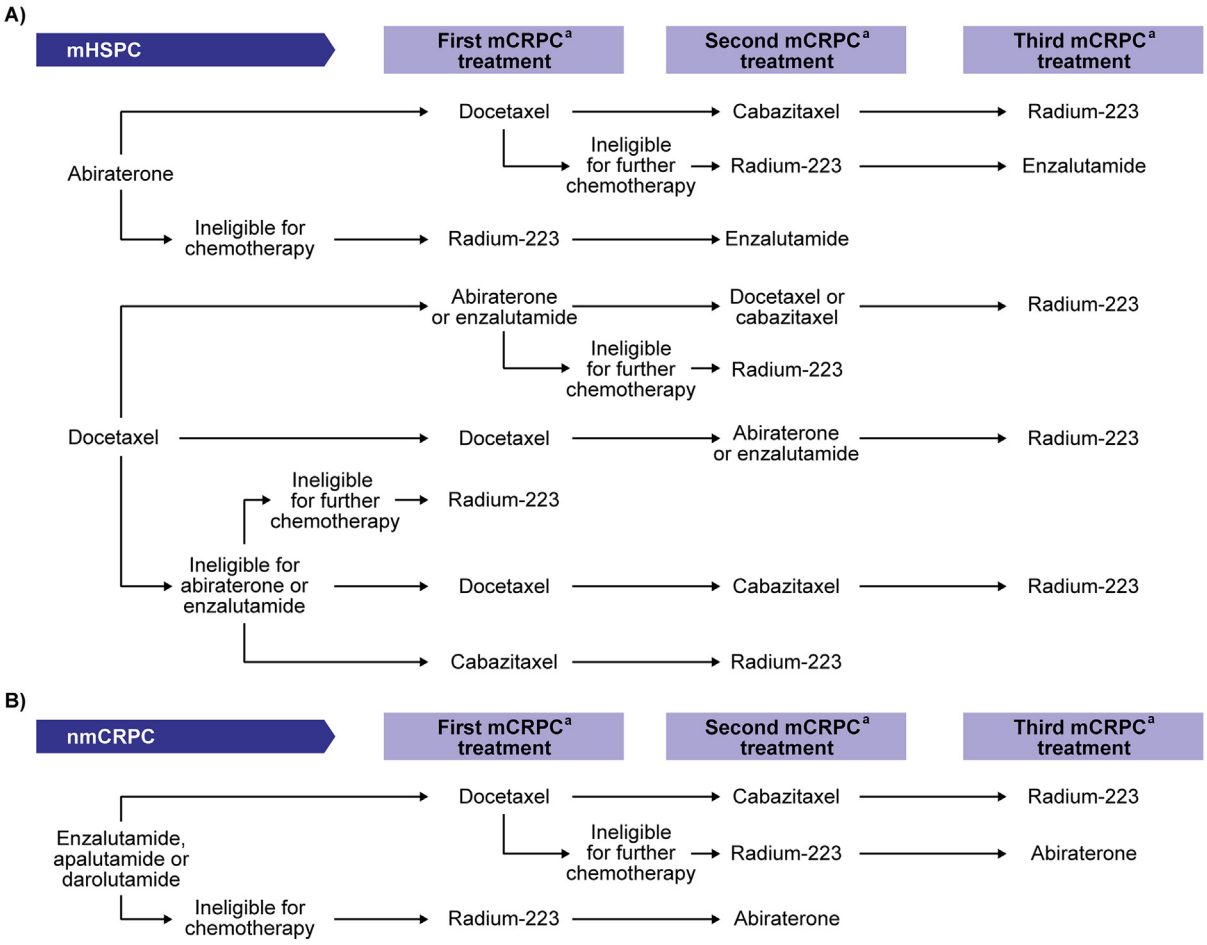


**Fig. 3 – Systemic therapies after progression in the mHSPC or nmCRPC settings. Potential sequencing options for approved life-prolonging agents following progression on (A) abiraterone or docetaxel for mHSPC, and (B) enzalutamide, apalutamide, or darolutamide for nmCRPC. These are illustrative algorithms based on the revised EU indication for radium-223. Not all potential treatment options are shown. Concurrent use of bone health agents is recommended to treat osteoporosis or for patients with bone metastases. Sequential use of abiraterone and enzalutamide (or vice versa) or apalutamide or darolutamide and abiraterone or enzalutamide is not considered an option due to likely futility of treatment. Consider clinical trials or best supportive care after all available systemic therapies have been administered. EU = European Union; mCRPC = metastatic castration-resistant prostate cancer; mHSPC = metastatic hormone-sensitive prostate cancer; nmCRPC = nonmetastatic castration-resistant prostate cancer. [a] mCRPC with bone metastases and no visceral metastases.**

Radium-223 specifically targets newly formed bone and is not effective against soft-tissue disease due to its unique mechanism of action. As such, patients with visceral metastases are not eligible for radium-223 treatment. Patients should ideally be offered radium-223 relatively early in the mCRPC treatment paradigm when they have bone-dominant disease (similar to patients in the ALSYMPCA study). Radium-223 should be offered prior to development of visceral metastases, which occur later in the disease course [36], at which point patients will miss the opportunity to receive a life-prolonging and well-tolerated treatment.

In ALSYMPCA, 43% of patients had received no prior docetaxel, and radium-223 was efficacious and well tolerated irrespective of prior chemotherapy status [60]. Therefore, we consider radium-223 to be a valuable treatment option for patients in both the pre- and the post-docetaxel setting. Importantly, patients who received chemotherapy following radium-223 treatment had stable haematological parameters overall [61], indicating that chemotherapy can safely be administered after radium-223.

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee recommended, based on an unplanned analysis of the ERA 223 trial, that the combination of radium-223 and abiraterone be contraindicated; this contraindication was subsequently implemented in the EU [18]. In addition, in the EU, radium-223 is now indicated for use after at least two prior lines of systemic therapy for mCRPC (excluding LHRH analogues) or for patients who are ineligible for other systemic treatments [18]. Of note, the radium-223 indication remains unchanged in the USA, Canada, Switzerland, and Japan.

While some patients will derive benefit from radium-223 after they have already received two lines of systemic therapy for mCRPC, this position could be suboptimal for many. As highlighted in our recent letter to the editor in *European Urology* [62] and during the discussion of the ERA 223 presentation at the 2018 annual

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ESMO congress, patients who have received two lines of therapy for mCRPC are late in the disease course and more likely to have developed visceral disease, therefore missing the window of opportunity to receive radium-223 therapy. Patients at this point would also have a greater disease burden, poorer performance status, and reduced haematological function, making them less likely to be able to complete radium-223 therapy. Retrospective analyses have demonstrated that completion of six radium-223 injections is associated with significantly improved overall survival [63,64]. We recommend considering radium-223 therapy for patients who align to the ALSYMPCA patient population, with bone-dominant disease, and whose quality of life will be improved with treatment. Furthermore, the likelihood of completing radium-223 treatment should be considered.

Based on the updated EU indication, it seems that now two overall populations of mCRPC patients are able to receive radium-223 in the EU: patients who have received two prior systemic mCRPC therapies and who are still able to benefit from radium-223, and patients who are unable to receive further systemic treatments, for example, due to likely futility of a second antihormonal therapy, existing comorbidities or frailty, or patient preference to avoid certain treatments. In line with the new EU indication and the considerations on treatment sequencing discussed above, we propose a number of potential treatment sequences for patients with mCRPC in the EU (Figs. 2 and 3).

## 7. Summary

The results from the ERA 223 study highlight the importance of randomised controlled clinical trials for evaluating novel therapeutic combinations. The results also reinforce the importance of monitoring and maintaining bone health in patients with prostate cancer. Consideration of bone health should begin as soon as patients initiate ADT. Despite the ERA 223 study outcome, radium-223 remains a valuable treatment option for patients with mCRPC and bone metastases. The revised EU indication reduces the proportion of patients able to receive radium-223 compared with those for whom radium-223 would be an ideal treatment, thus limiting the treatment options for a group of patients for whom there is an ongoing unmet need. However, for patients who are ineligible for other systemic treatments, and given that sequential use of antihormonal agents should be avoided, radium-223 may still be given at an earlier point in the disease course, allowing these patients the chance to achieve optimal treatment outcomes.

***Author contributions***: Joe M. O'Sullivan had full access to all the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design:* O'Sullivan, Carles, Cathomas, Gomez-Iturriaga, Heinrich, Kramer, Ost, van Oort, Tombal.
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*Analysis and interpretation of data:* None.
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