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The role of radium-223 in the evolving treatment landscape of metastatic castration-resistant prostate cancer: A narrative review

Álvaro Pinto [a,*], Mario Domínguez [b], Alfonso Gómez-Iturriaga [c], Alejo Rodriguez-Vida [d], Juan Antonio Vallejo-Casas [e], Elena Castro [f]

[a] Medical Oncology Department, Hospital Universitario La Paz, Madrid, Spain
[b] Urology Department. Hospital Universitario Marqués de Valdecilla, Instituto de Investigación de Valdecilla (IDIVAL), Santander, Spain
[c] Radiation Oncology Department, Cruces University Hospital, Biobizkaia Health Research Institute, Basque Country University (UPV/EHU), Bilbao, Spain
[d] Medical Oncology Department, Hospital Del Mar, CIBERONC, Barcelona, Spain
[e] UGC Nuclear Medicine. Hospital Universitario Reina Sofía, Córdoba, Spain
[f] Medical Oncology Department, Hospital Universitario 12 de Octubre, Madrid, Spain

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ABSTRACT

The treatment of metastatic castration-resistant prostate cancer (mCRPC) has been rapidly evolving over the last two decades. The advent of new androgen receptor pathway inhibitors (ARPIs) such as abiraterone acetate or enzalutamide marks a great advance for treating mCRPC patientd in the pre- and post-docetaxel settings. The subsequent approval of ARPIs in early stages—i.e., metastatic hormone-sensitive (mHSPC) or nonmetastatic CRPC—led to a realignment of subsequent treatment choices upon progression to mCRPC, given the possibility of cross-resistance between ARPIs. Therapies with mechanisms of action different from those of ARPIs are now the focus of new treatment developments. Also, this anomalous situation brings the focus back to well-known treatments currently used later in the treatment sequence. This is the case of radium-223 which, when administered with enzalutamide, has recently been shown to prolong radiographic progression-free survival vs. enzalutamide alone in the first line in asymptomatic or mildly symptomatic patients with no known visceral metastases. In this narrative review, we summarize the treatment landscape for mCRPC, both from a historical and practical point of view, to understand the new potential of radium-223 as a treatment option in this setting.

1. Introduction

The treatment of metastatic prostate cancer (PC) has been rapidly evolving over the last two decades. Since the advent of the new androgen receptor (AR) pathway inhibitors (ARPIs) abiraterone acetate/prednisone (de Bono et al., 2011, Ryan et al., 2015) and enzalutamide (Scher et al., 2012, Beer et al., 2014) for the treatment of metastatic castration-resistant PC (mCRPC) on top of background androgen deprivation therapy (ADT, mainly with luteinizing hormone-releasing hormone [LHRH] agonists), new therapies are continuously emerging in this setting. Expanding treatment options makes medical management more complex, especially given the absence of validated predictive biomarkers and the lack strong evidence supporting the optimal sequence (Maurice Dror et al., 2021). In recent years, the mCRPC landscape has become even more complex owing to the use of ARPIs in earlier stages, such as in the metastatic hormone-sensitive (mHSPC)—alone (abiraterone acetate/prednisone (James et al., 2017, Fizazi et al., 2017), enzalutamide (Armstrong et al., 2019, Davis et al., 2019), or apalutamide (Chi et al., 2019, Chi et al., 2021)) or in combination with docetaxel (darolutamide (Smith et al., 2022a) or abiraterone acetate/-prednisone (Fizazi et al., 2022))—and the non-metastatic (M0) CRPC (nmCRPC) stages (enzalutamide (Hussain et al., 2018), apalutamide (Smith et al., 2018b), and darolutamide (Fizazi et al., 2019)). The early use of ARPIs and docetaxel has led to a realignment of subsequent treatment choices upon progression to mCRPC, given the possibility of cross-resistance between ARPIs. Treatment decisions are hampered because landmark trials proving the benefit of these options did not include patients representative of the population now seen in clinical practice. This scenario fosters the development of therapies with mechanisms of action that are different from those of ARPIs, and brings the focus back to those now relegated for use late in the treatment sequence (i.e., radium-223). At the same time, new evidence is

* Correspondence to: Medical Oncology Department, Hospital Universitario La Paz, P.º de la Castellana, 261 Fuencarral-El Pardo, Madrid 28046, Spain.
E-mail address: alvaropintomarin@gmail.com (Á. Pinto).

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continuously emerging, with new combinations and sequences being explored, reshaping treatment algorithms yet again.

In this narrative review, we summarize the treatment landscape for mCRPC, both from a historical and practical point of view, to understand the new potential of radium-223 as a treatment option in this setting.

2. Treatment of mCRPC: How did we get here?

2.1. From symptomatic control improved survival and the advent of ARPIs

For nearly a decade, chemotherapy with docetaxel administered every three weeks was the only treatment that had proved to prolong overall survival (OS) vs. mitoxantrone (both administered with prednisone) in men with mCRPC progressing on ADT (TAX 327 trial) (Tannock et al., 2004). Before this trial, mitoxantrone (given with low-dose prednisone or hydrocortisone) and steroids were considered the standard of care (SoC) for mCRPC, with mitoxantrone having greater symptomatic control than steroids alone (Tannock et al., 1996, Kantoff et al., 1999). Treatment with docetaxel also reduced pain and the serum prostate-specific antigen (PSA) levels, and improved health-related quality of life (HRQoL). However, the rate of adverse events was higher than with mitoxantrone (Tannock et al., 2004). Some years later, the results of the randomized, open-label, phase 3 TROPIC trial positioned the taxane cabazitaxel as an alternative for docetaxel-resistant tumors, with longer median OS (primary endpoint) and radiographic progression-free survival (rPFS) vs. mitoxantrone (de Bono et al., 2010). At the same time, the vaccine sipuleucel-T showed an OS benefit in patients with asymptomatic or minimally symptomatic mCRPC, 15 % of whom had received docetaxel (Kantoff et al., 2010), thereby moving docetaxel to a subsequent treatment line. This was the first immunotherapy showing efficacy in mCRPC, although no benefit in rPFS was observed. Sipuleucel T is not licensed for mCRPC in Europe.

At the beginning of the last decade, two randomized, phase 3 trials showed the benefit on OS of the ARPIs abiraterone acetate/prednisone (COU-AA-301 trial) (de Bono et al., 2011) and enzalutamide (AFFIRM trial) (Scher et al., 2012) in patients who had progressed on docetaxel. Shortly after, two other randomized, phase 3 trials with enzalutamide (PREVAIL trial) (Beer et al., 2014) and abiraterone acetate/prednisone (COU-AA-302 trial) (Ryan et al., 2015) also demonstrated and OS benefit in asymptomatic or mildly asymptomatic docetaxel naïve men with good performance status (ECOG PS 0–1). Since then, ARPIs are the first-line of treatment owing to their efficacy and better tolerability profile, especially considering that many patients may not be eligible for docetaxel due to old age, frailty, or comorbidities (Cornford et al., 2024, NCCN, 2024) (Fig. 1).

2.2. ARPI treatment ¿and retreatment?

Despite the benefits offered by ARPIs, it should be noted that nearly one-third of patients treated with abiraterone and 25 % of those treated with enzalutamide show primary resistance to these agents (Buttigliero et al., 2015). However, tumors treated with abiraterone or enzalutamide may also acquire resistance while on treatment through multiple resistance mechanisms (Galletti et al., 2017, Pinto et al., 2022). Resistance mechanisms to apalutamide or darolutamide are less known, but some are common to the four ARPIs (Pinto et al., 2022, Zhao et al., 2020). The resistance mechanisms are multiple and include, among others, intratumoral androgen production, amplification, mutation, or expression of the AR splice variants (truncated AR protein that is constitutively active without the need of a ligand), increased steroidogenesis, upregulation of signals downstream of the AR (e.g., CYP17), and development of androgen-independent tumor cells (Galletti et al., 2017, Pinto et al., 2022).

Having acquired resistance to an ARPI would not be a problem were it not because their overlapping mechanisms generate cross-resistance to other ARPIs (Galletti et al., 2017, Pinto et al., 2022). The randomized, open-label, phase 2 crossover ABI-ENZA trial was the first prospective trial to evaluate both sequences and estimate the degree of cross-resistance in patients with mCRPC. In this trial, the time to second PSA progression was longer for the sequence of abiraterone followed by enzalutamide (group A) than for enzalutamide followed by abiraterone (group B), with a median of 19.3 vs. 15.2 months (Hazard ratio [HR] 0.66, 95 % confidence interval [CI] 0.45–0.97; P = 0.036). This effect might be driven by the improved activity of enzalutamide vs. abiraterone as a second treatment line, with a median time to PSA

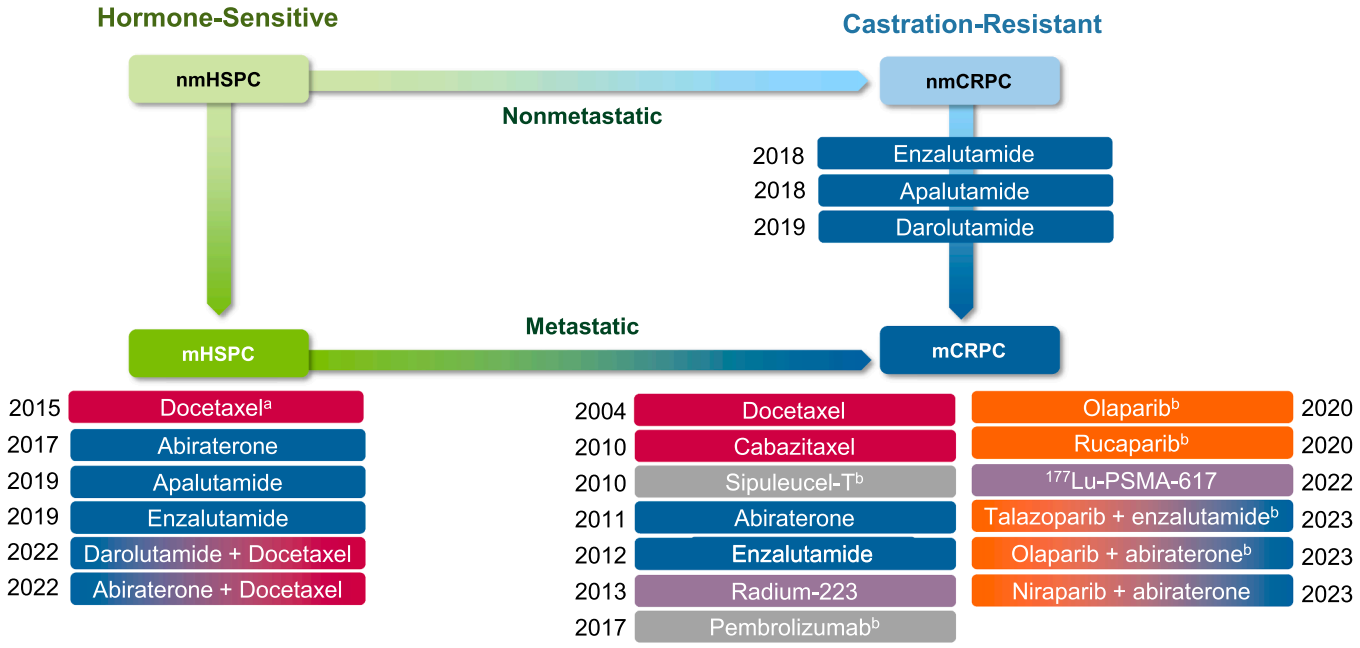

Fig. 1. Current therapeutic options in mCRPC: where patients may come from. [a]Only approved in the EU. [b]Only approved in the US. ARPI, androgen receptor pathway inhibitor; CRPC, castration-resistant prostate cancer; HSPC, hormone-sensitive prostate cancer; m, metastatic, nm, nonmetastatic; PARPi, poly (ADP-ribose) polymerase inhibitor; PSMA, prostate-specific membrane antigen.

progression in patients who progressed and crossed over of 3.5 months vs.1.7 months and a rate of confirmed PSA decline of 36 % vs. 4 %; P < 0.001. Of note, patients with a short time to progression on the first-line ARPI (<3 months) were less likely to benefit from the second-line ARPI (Khalaf et al., 2019).

In this setting of widespread use of ARPIs at the mCRPC stage, the randomized, open-label, phase 3 CARD trial showed the value of cabazitaxel over retreatment with the alternative ARPI in patients who had previously received docetaxel and either enzalutamide or abiraterone (HR 0.54; 95 % CI 0.40–0.73; P < 0.001), and was the first trial to demonstrate a survival benefit in the third treatment line. The median imaging-based PFS (primary endpoint) was 8.0 months with cabazitaxel and 3.7 months with the ARPIs. Cabazitaxel also improved OS vs. the alternative ARPI. The rate of grade ≥ 3 adverse events was similar in both arms, although the occurrence of adverse events leading to treatment discontinuation was higher for cabazitaxel (19.8 % vs. 8.9 %) (de Wit et al., 2019).

2.3. Targeting bone metastases and improving survival

Metastatic CRPC affects the bone marrow from early stages, leading to metastases and symptomatic skeletal events (SSEs) such as spinal cord compression, pathological fractures, and pancytopenia. The treatment of bone metastases in mCRPC had been focused mainly on palliative care with bone-protecting agents (BPA) like bisphosphonates or denosumab, and external radiation and beta-emitting radiopharmaceuticals like strontium-89 and samarium-153. However, none offered any survival benefit, and the use of radiopharmaceuticals was limited by bone marrow toxicity (Coleman et al., 2020). In 2013 the ALSYMPCA trial demonstrated an OS benefit with the alpha emitter radium-223 plus SoC vs. SoC alone in patients with symptomatic bone metastases and no known visceral metastases who failed or were unfit for docetaxel (Parker et al., 2013).

Radium is a bone-seeking calcium mimetic that selectively binds to areas of increased bone turnover in bone metastases (Henriksen et al., 2003). It emits high-energy alpha particles of short range (<100 μm) (Bruland et al., 2006) that induce breaks in the double-stranded helix of DNA, resulting in a highly localized cytotoxic effect with minimum impact in adjacent tissues (Liepe, 2009, Suominen et al., 2017).

In the ALSYMPCA trial, the benefit of radium-223 extended to secondary endpoints, such as the time to the first SSE, the time to an increase in the total alkaline phosphatase level, and the time to the rise in the PSA level, regardless of prior chemotherapy. Radium-223 was also well tolerated, with low myelosuppression rates and no clinically meaningful differences in the frequency of grade 3–4 adverse events (Parker et al., 2013). A significantly higher percentage of patients in the radium-223 arm showed a meaningful improvement in HRQoL (i.e., an increase in the total FACT-P score of ≥10) while on treatment: 25 % vs. 16 % with placebo, P = 0.02 (Parker et al., 2013). The improvement was consistent across multiple HRQoL domains (four of five FACT-P subscales, except for social well-being). Similar results were observed in the EQ-5D utility score: 29.2 % vs. 18.5 %, respectively; P = 0.004. Prior docetaxel use, and current BPA use did not affect these findings (Nilsson et al., 2016). In a subsequent sub-analysis, radium-223 also showed a reduction in the risks for external beam radiation therapy for bone pain and spinal cord compression (Sartor et al., 2014). A three-year follow-up showed that radium-223 remained well tolerated, with low myelosuppression, and very few non-hematologic adverse events or new safety concerns (Parker et al., 2017). Radium-223 emerged thus as an alternative to docetaxel in such patients.

Shortly after radium-223 became available, the phase 3 ERA 223 trial evaluated the benefit of the early use of radium-223 plus abiraterone acetate/prednisone—which had proven to improve OS and rPFS in chemotherapy-naïve mCRPC with few or no symptoms (Ryan et al., 2015) — in chemotherapy-naïve mCRPC patients with bone metastases with no or only mild symptoms. In this trial, adding radium-223 to abiraterone acetate/prednisone resulted in no improvement of OS and, moreover, led to increased frequency of bone fractures compared to abiraterone alone. Since these results were first published (Smith et al., 2018a), the European Medicines Agency (EMA) issued a formal warning against the use of radium-223 in combination with abiraterone in men with mCRPC, and restricted its use to patients who have had two previous treatments for mCRPC (3rd line) or who cannot receive other treatments. The US Food and Drug Administration (FDA) includes this risk as a warning (Table 1).

3. Treatment approaches in early stages complicate subsequent management decisions in mCRPC

The treatment options discussed above shaped the landscape of mCRPC treatment until 2017, with docetaxel, enzalutamide, abiraterone acetate/prednisone, and sipuleucel-T (outside Europe) being the first-line of treatment, followed by the two ARPIs, docetaxel and radium-223 in the second line, and cabazitaxel in the third line. That year, the first landmark study demonstrated the benefit on rPFS and OS of adding abiraterone acetate/prednisone to background ADT in men with mHSPC (James et al., 2017, Fizazi et al., 2017). Enzalutamide (Armstrong et al., 2019, Davis et al., 2019) and apalutamide (Chi et al., 2019, Chi et al., 2021) followed. Shortly after, abiraterone acetate/prednisone and darolutamide also showed an OS benefit in patients with mHSPC when used as triplet therapy with ADT and docetaxel in the PEACE-1 (Fizazi et al., 2022) and ARASENS (Smith et al., 2022a) studies, respectively. Patients with synchronous disease represented 100 % of the population in the PEACE-1 trial and 87 % in the ARASENS trial. This treatment replaced the previous treatment intensification with the doublet docetaxel plus ADT (Sweeney et al., 2015, James et al., 2016). In parallel, apalutamide (Smith et al., 2018b), enzalutamide (Hussain et al., 2018), and darolutamide (Fizazi et al., 2019) also demonstrated a benefit on metastases-free survival-free metastasis (MFS) in men with nmCRPC at high risk of metastases. As a result, in the following years, upon progression to mCRPC, many patients would have been exposed to at least one ARPI and probably to docetaxel (Fig. 1).

Most evidence on the resistance to an ARPI after progression on another ARPI emerges from studies in the mCPRC setting (i.e., second-line treatment). In contrast, evidence in the mHSPC setting is scarce. It can be assumed that this resistance may also occur when the first ARPI is used in the mCSPC or nmCRPC settings (Maurice Dror et al., 2021, Cornford et al., 2024) In any case, considering this cross-resistance risk argues against the sequential use of treatments with the same or overlapping mechanisms of action (Buck et al., 2021). The guidelines of the European Association of Urology (EAU) recommend not to sequence abiraterone and enzalutamide, particularly 'if the time of response to ADT and to the first ARPI was short (≤ 6 – 12 months) and high-risk features of rapid progression are present.' (Cornford et al., 2024).

4. Searching for non-overlapping mechanisms of action

Besides radium-223 and sipuleucel-T (outside Europe), whose mechanisms of action do not overlap with those of ARPIs, other drugs with novel mechanisms of action have been investigated and approved in recent years to provide treatment options beyond ARPIs and docetaxel in the first line and beyond. These are commented on below.

4.1. PARP inhibitors

One of the advances in the mCRPC setting are the Poly (ADP-ribose) polymerase (PARP) inhibitors (PARPis), especially in tumors with germline and somatic genomic alterations of genes involved in DNA damage repair (DDR) by homologous recombination (HRR). These include mutations in genes such as *BRCA2* (5.3 %), *ATM* (1.6 %], *CHEK2* (1.9 %), *BRCA1* (0.9 %), *RAD51D* (0.4 %), and *PALB2* (0.4 %) (Pritchard et al., 2016), which have been associated with more

Table 1
Indications for the use poly (ADP-ribose) polymerase inhibitors (PARPIs) and radiopharmaceuticals licensed in prostate cancer. Recommendations of use from the EAU y NCCN Guidelines.

	Indications		Recommendations	
	European Medicines Agency	**US Food & Drug Administration**	**EAU Guidelines** (Cornford et al., 2024)	**NCCN Guidelines** (NCCN, 2024)
Poly (ADP-ribose) polymerase inhibitors (PARPis)				
Olaparib	• As monotherapy for the treatment of adult patients with mCRPC and *BRCA*1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included an ARPI. • In combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated (EMA, 2019).	• Treatment of adult patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC who have progressed following prior treatment with enzalutamide or abiraterone (FDA, 2020a).	• First-line treatment: In combination with abiraterone in patients previously untreated for mCRPC and harbouring an HRR or *BRCA* mutation if the patient is fit for both agents (Strong) • Second-line treatment: Patients with mCRPC and progression following docetaxel chemotherapy in case of DNA HRR alterations (Strong)	• First-line treatment: In combination with abiraterone in: Patients with *BRCA* mutation and no prior docetaxel/no prior novel hormone therapy (category 1). Patients with *BRCA* mutation progressing on prior docetaxel/ no prior novel hormone therapy • Second-line treatment: Patients with *BRCA* 1/2 mutation (category 1) or HRR mutation other than *BRCA* 1/2 progressing on prior novel hormone therapy/ no prior docetaxel. • Third-line treatment: Patients with HRR mutation progressing on prior docetaxel and a novel hormone therapy (category 1)
Rucaparib	-	• Adult patients with a deleterious *BRCA* mutation (germline and/or somatic)-associated mCRPC who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy* (FDA, 2020b)	(See footnotes)	• Second-line treatment: Patients with *BRCA* 1/2 mutation progressing on prior novel hormone therapy/ no prior docetaxel (category 1) • Third-line treatment: Patients with *BRCA* 1/2 mutation progressing on prior docetaxel and a novel hormone therapy.
Niraparib + abiraterone acetate	• With prednisone or prednisolone for the treatment of adult patients with mCRPC and *BRCA* 1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated (EMA, 2024a).	• With prednisone for the treatment of adult patients with deleterious or suspected deleterious *BRCA*-mutated mCRPC (FDA, 2023a).	• First line treatment: Patients previously untreated for mCRPC and harbouring a *BRCA* mutation if the patient is fit for both agents (Strong)	• First-line treatment: Patients with *BRCA* mutation and no prior docetaxel/no prior novel hormone therapy (category 1) • Second-line treatment: Patients with *BRCA* mutation progressing to prior docetaxel/no prior novel hormone therapy. Patients with *BRCA* mutation progressing to prior novel hormone therapy/no prior docetaxel (category 2B).
Talazoparib	• In combination with enzalutamide for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated (EMA, 2024b).	• In combination with enzalutamide for the treatment of adult patients with HRR gene-mutated mCRPC (FDA, 2023b).	• First-line treatment: In combination with enzalutamide in patients previously untreated for mCRPC and harbouring an HRR-mutation if the patient is fit for both agents (Strong)	• First-line treatment: In combination with enzalutamide in patients with HRR mutation and no prior docetaxel/no prior novel hormone therapy (category 1) • Second-line treatment: Patients with HRR mutation progressing to prior docetaxel/no prior novel hormone therapy. Patients with HRR mutation progressing to prior novel hormone therapy/no prior docetaxel (category 2B).
Radiopharmaceuticals				
Radium−223	• In monotherapy or in combination with LHRH analogue for the treatment of adult patients with mCRPC, symptomatic bone metastases and no known visceral metastases, in progression after at least two prior lines of systemic therapy for mCRPC (other than LHRH analogues), or ineligible for any available systemic mCRPC treatment (EMA, 2024c)	• Treatment of patients with mCRPC, symptomatic bone metastases and no known visceral metastatic disease (FDA, 2019)	• Patients with mCRPC and progression following docetaxel chemotherapy (Strong)	• Patients with symptomatic bone metastases with no prior docetaxel/no prior novel hormone therapy or progressing to one or both treatments (category 1)
177 Lutetium-PSMA−617	• In combination with ADT with or without AR pathway inhibition is indicated for the treatment of adult patients with progressive PSMA-	• Treatment of adult patients with PSMA-positive mCRPC)who have been treated with AR pathway	(See footnotes)	• Patients with PSMA-positive metastases (category 1)

(*continued on next page*)

Table 1 (*continued*)

Indications		Recommendations	
European Medicines Agency	**US Food & Drug Administration**	**EAU Guidelines** (Cornford et al., 2024)	**NCCN Guidelines** (NCCN, 2024)
positive mCRPC who have been treated with AR pathway inhibition and taxane-based chemotherapy (EMA, 2022).	inhibition and taxane-based chemotherapy (FDA, 2022)		

ADT, androgen deprivation therapy; AR, androgen receptor; EAU, European Association of Urology; HRR, homologous recombination repair; LHRH, luteinising hormone releasing hormone; mCRPC, metastatic castration-resistant prostate cancer; NCCN, National Comprehensive Cancer Network; PSMA, prostate-specific membrane antigen.

*Indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

EAU: Base the choice of treatment on the performance status (PS), symptoms, comorbidities, location and extent of disease, genomic profile, patient preference, and on previous treatment for hormone-sensitive metastatic prostate cancer (mHSPC).(alphabetical order: abiraterone, cabazitaxel, docetaxel, enzalutamide, ^{177}lutetium-PSMA-617-radioligand therapy, radium-223, sipuleucel-T, and for patients with DNA HRR alterations olaparib, olaparib/abiraterone, niraparib/abiraterone, rucaparib, talazoparib/enzalutamide).

aggressive and lethal disease (Castro et al., 2013, Na et al., 2017, Castro et al., 2019). The indications for these PARPis and how the main guidelines on PC management recommend their use is shown in Table 1.

Two PARPis (olaparib and rucaparib) have been demonstrated to prolong imaging-based (ib) PFS in mCRPC tumors with alterations in specific HRR genes, especially in *BRCA1/2*. The phase 3 trial PROfound trial demonstrated a longer median image-based progression-free survival (ibPFS) with olaparib vs. enzalutamide or abiraterone acetate/prednisone retreatment in men with mCRPC with an HRR alteration (*BRCA1/2* or *ATM*) who had progressed on these ARPIs (most of them also to chemotherapy): HR 0.34; 95 % CI, 0.25–0.47; P < 0.001 (de Bono et al., 2020). In the final analysis of OS, this was also longer with olaparib (HR 0.69; 95 % CI, 0.50–0.97; P = 0.02). The most frequent adverse events in both cohorts were anemia and nausea (Hussain et al., 2020). The phase 3 TRITON 3 trial confirmed the benefit of rucaparib over physician's choice (docetaxel or abiraterone/enzalutamide) in patients who had progressed on an ARPI, 75 % of whom had a *BRCA* mutation. The median ibPFS was significantly longer with rucaparib vs. the physician's choice both in the subgroup of patients with a *BRCA* mutation (HR 0.50; 95 % CI, 0.36–0.69; P < 0.001) and the intention-to-treat population (HR 0.61; 95 % CI, 0.47–0.80; P < 0.001). Fatigue and nausea were the most common adverse events reported with rucaparib (Fizazi et al., 2023) (Fig. 1).

Based on a possible synergistic antitumor effect when combining PARPis and ARPIs, three randomized, phase 3 trials have evaluated the benefit of PARPis as a first-line treatment in combination with an ARPI (enzalutamide or abiraterone) in patients with and without HRR alterations (Fig. 1). In the PROpel trial, the combination of abiraterone acetate/prednisone with olaparib demonstrated a significantly longer median ibPFS for vs. abiraterone acetate/prednisone plus placebo in an HRR unselected population (HR 0.66; 95 % CI, 0.54–0.81; P < 0.001) (Clarke et al., 2022). In the preplanned final analysis, abiraterone plus olaparib showed a trend to a longer median OS (HR 0.81, 95 % CI 0.67–1.00, P = 0.0544). The most common grade 3–4 adverse event was anemia (16 % in the combination therapy group vs. 3 % in the placebo plus abiraterone acetate/prednisone group) (Saad et al., 2023). In the randomized, phase 3 TALAPRO-2 trial, the combination of enzalutamide plus talazoparib demonstrated a significantly longer rPFS vs. enzalutamide plus placebo in the unselected all-comer cohort (HR 0.63; 95 % CI 0.51–0.78; P < 0.0001). The benefit of the combination was greater in the HRR+ vs. HRR- subgroup (HR 0.46; 95 % CI 0.30–0.70; P < 0.001). Recently, an OS benefit has also been reported (HR 0.79; 95 % CI, 0.661–0.958; P = 0.0155) (Agarwal et al., 2025). The most common grade 3–4 adverse event with talazoparib was anemia (Agarwal et al., 2023). In the randomized, phase 3 MAGNITUDE trial, the median rPFS was significantly longer with abiraterone plus niraparib vs. abiraterone plus placebo in the subgroup of patients with *BRCA1/2* mutations (primary outcome) and the overall HRR+ group (HR 0.55, 95 % CI 0.39–0.78; P = 0.0007 and HR 0.76, 95 % CI 0.60–0.97; P = 0.0280, respectively). The most frequent adverse events for combination therapy were anemia and hypertension (Chi et al., 2023a). In the final analysis, after a median follow-up of 35.9 months, OS was longer with the combination vs. abiraterone alone (HR 0.79; 95 % CI 0.55–1.12, P = 0.18). In a prespecified multivariate analysis for OS that addressed baseline imbalances, OS also favored the combination (HR 0.66; 95 % CI 0.46–0.95, P = 0.02) (Chi et al., 2023b).

Two open-label phase 2 trials (TALAPRO-1 and GALAHAD) have shown promising preliminary results for talazoparib (de Bono et al., 2021) and niraparib (Smith et al., 2022b) as monotherapy in heavily pretreated HRR+ mCRPC patients.

4.2. Radiopharmaceuticals

Theranostics—a term that combines therapeutics and diagnostics—is probably one of the most exciting novelties in the mCRPC setting. This term refers to combining two radiopharmaceutical agents containing radionuclides, one to identify (diagnose) and a second to deliver therapy (treat) to the primary tumor and any metastatic site (Burkett et al., 2023). When used therapeutically, they can be combined with α- or β-emitting radioisotopes, with the former being larger and inflicting more damage than the latter (O'Dwyer et al., 2021). They can also be combined with Auger emitters, which have an even shorter range than α-particle emitters (Shen et al., 2020). The α-emitter radium-223 was the first radiopharmaceutical to demonstrate an OS benefit in patients with mCRPC (Parker et al., 2013) (Fig. 1).

^{177}Lu-PSMA-617 is a radioligand therapy that delivers β-particle radiation to prostate-specific membrane antigen (PSMA) expressing cells. In the phase 3, randomized, open-label VISION trial, conducted in patients with ^{68}Ga-PSMA+ mCRPC previously treated with at least one ARPI and one or two taxane-based regimens, ^{177}Lu-PSMA-617 plus SoC showed significantly longer ibPFS vs. SoC alone (HR 0.40; 99.2 % CI, 0.29– 0.57; P < 0.001). Median OS —the alternate primary endpoint— also improved (15.3 vs. 11.3 months; HR, 0.62; 95 % CI, 0.52–0.74; P < 0.001). The incidence of grade ≥ 3 adverse events was higher fo ^{177}Lu -PSMA-617 (52.7 % vs. 38.0 % for SoC alone) (Sartor et al., 2021). The efficacy and safety of ^{177}Lu-PSMA-617 has also been compared to that of cabazitaxel in patients with PSMA+ mCRPC pretreated with docetaxel and for whom cabazitaxel was considered the next appropriate SoC. In the unblinded, randomized phase 2 TheraP trial, the rate of PSA response (PSA50) was 66 % with ^{177}Lu-PSMA-617 vs. 37 % with cabazitaxel, by intention-to-treat (difference 29 %, 95 % CI: 16–42; P < 0.001) and 66 % vs. 44 % by treatment received (difference 23 %, 95 % CI 9–37; P = 0.0016). Grade 3–4 adverse events were more frequent for cabazitaxel (53 % vs. 33 % for ^{177}Lu-PSMA-617) (Hofman et al., 2021). No differences in OS have been reported in a subsequent analysis with mature follow-up for OS (Hofman et al., 2024).

Another trial, the randomized, open-label, phase 3PSMAfore trial, assessed the value of ^{177}Lu-PSMA-617 vs. ARPI retreatment in taxane-naïve patients. This trial showed a significantly longer median rPFS for ^{177}Lu-PSMA-617 vs. ARPI retreatment (HR 0.49; 95 % CI 0.39–0.61). At the moment of the analysis, 137 (57 %) patients allocated to the ARPI change group had crossed over to ^{177}Lu-PSMA-617 (78 % of patients with radiographic progression). No difference was observed in OS (HR 0.98, 95 % CI 0.75–1.28; P = 0.44). The incidence of grade ≥ 3 adverse events was lower with ^{177}Lu-PSMA-617 vs. abiraterone/enzalutamide (36 % vs. 48 %) (Morris et al., 2024) **(**Fig. 1**)**. The indication for and how the main guidelines on PC management recommend the use of ^{177}Lu-PSMA-617 is shown in Table 1.

5. Looking back to radium-223

Treatment options whose mechanisms of action differ from those of ARPIs are currently the focus of research. For this reason, the role of radium-223 in mCRPC has received significant interest as an option in the early lines of treatment.

5.1. What was known

After the warning issued by the EMA due to the increased risk of bone fractures for the combination of radium-223 and abiraterone in the ERA 223 trial, a retrospective study investigated the use of radium-223 with abiraterone or enzalutamide in clinical practice. Treatment could be either in a layered or a concurrent fashion. This study showed that the use of the combination radium-223 plus ARPI was frequent (136/625 [22 %] patients with abiraterone and 167/625 [27 %] with enzalutamide), especially in the layered fashion (77 % of patients). Of note, 67 % of these patients had received prior BPA, and 55 % received concomitant BPA. The incidence rates for SSEs were reduced when BPAs were used. The investigators highlighted the underuse of BPA in clinical practice when using radium-223 combined with either abiraterone or enzalutamide (Shore et al., 2020).

Other real-world evidence studies have provided data on the use of radium-223 in clinical practice. These have been conducted in heterogeneous populations, including patients with comorbidities, used concomitant hormonal treatments and extensive prior treatments. Radium-223 was well tolerated in these studies, with no new safety concerns, independently of concurrent use with abiraterone or enzalutamide (Sartor et al., 2018, Shore et al., 2020). Some of them are still ongoing (Badrising et al., 2020, Seront et al., 2020, Kuppen et al., 2020, George et al., 2022, Palmedo et al., 2023, Anido-Herranz et al., 2024, Huang et al., 2024) **(**Table 2**).**

Among them, the ongoing observational REASSURE trial, that began in 2014, evaluates the real-world, long-term safety and effectiveness of radium-223 in patients with mCRPC and bone metastases. Results from the pre-specified interim analysis after a median follow-up of 11.5 months, with 1465 patients who were evaluable, indicate that the safety profile of radium-223 was consistent with that of the clinical trials, with 35 % of patients reporting treatment-related adverse events and 21 % of serious treatment-emergent adverse events (TEAEs). Grade 3/4 hematological toxicities were present in 15 % of patients after completion of radium-223 therapy. Median OS from radium-223 initiation was 15.6 months (95 % CI 14.6–16.5). The risk of second primary malignancies was low (only 1 % during the follow-up period), although this was short). The safety profile of radium-223 was independent of prior, concomitant, or subsequent use of other systemic anticancer therapies or radiotherapy (Higano et al., 2023). A subsequent analysis was conducted in 182 chemotherapy-naive patients who started radium-223 and subsequently received taxane-based chemotherapy (90 % docetaxel) 'immediately' (starting ≤90 days, n = 73 [40 %]) or 'delayed' (>90 days, n = 109 [60 %]) after the last radium-223 dose. The incidence of hematologic adverse events was low (14 patients with grade 3/4 hematologic events during chemotherapy: 10 in the 'immediate' and four in the 'delayed' subgroup), thus supporting that taxane chemotherapy is a feasible option for those who progress on radium-223 (Higano et al., 2024).

Using different measurement scales, several studies have shown that radium-223 increases or at least does not adversely impair HRQoL (Sraieb et al., 2020, Badrising et al., 2022, van der Doelen et al., 2023).

What is new

Most of the latests evidence on the potential of radium-223 in mCRPC stems from the PEACE-3 trial. Similarly to the ERA 223 trial, the PEACE-3 trial compared the efficacy and safety of radium-223 in combination with a secondary hormonal therapy (enzalutamide) vs. secondary hormone therapy alone in enzalutamide- or radium-223 naïve patients with asymptomatic or mildly symptomatic mCRPC with bone metastases and with no known visceral metastases. Preliminary results showed that combining radium-223 with enzalutamide was associated with significant improvements in rPFS (primary endpoint) (median 19.4 vs.16.4 months; HR 0.69, 95 % CI: 0.54–0.87, P = 0.0009). An OS benefit was also observed with the combination vs. enzalutamide alone (median 42.3 vs. 35 months, respectively; HR 0.69, 95 % CI: 0.52–0.90, P = 0.0031). Benefits were also observed in key secondary outcomes such as the time to the next systemic treatment (HR: 0.57, 95 % CI: 0.44–0.75, P < 0.0001). The time to SSE was similar. Grade ≥ 3 hypertension (~34 %) was the most frequent adverse event with the combination (Gillessen et al., 2024). At the study entry, ~50 % of patients used a BPA. A study amendment made these mandatory, which increased BPA use to 97 % The cumulative incidence of fractures decreased greatly with these agents: from 37.1 % (95 % CI 21.3–53.0 %) to 2.7 % (95 % CI 0.5–8.5 %) in the combination arm and from 15.6 % (95 % CI 5.6–30.3 %) to 2.6 % (95 % CI 0.5–8.3 %) in the enzalutamide arm (Gillessen et al., 2025).

Recently, the RAPSON study has reported a greater improvement of HRQoL with radium-223 vs. docetaxel when these treatments are used after progression on an ARPI: mean change (SD) in FACT-P total scores from baseline to week 12: 4 (16.84) for radium-223 vs. 7.87 (14.08) for docetaxel. The sequence radium-223 -> docetaxel was also better tolerated (Brighi et al., 2024).

5.2. What is coming

Several ongoing studies are evaluating new combinations and therapeutic sequences with radium-223 that will redefine its potential **(**Table 3**)**

6. Critical view

Since the end of the last decade, the treatment landscape of patients with mCRPC has experienced a continuous change, with the early use of ARPIs in the metastatic hormone-sensitive and non-metastatic castration stages having impacted treatment decision-making after progression to mCRPC. The evidence supporting the likelihood of cross-resistance between ARPIs—the first-line treatment option in mCRPC—and the lack of evidence for their effectiveness in patients progressing on another ARPI has hindered the therapeutic decision-making process. In this context, therapies with mechanisms of action that do not overlap with those of ARPIs offer a potentially feasible treatment option. The recent results of the PEACE-3 trial, which showed the potential of combining enzalutamide with radium-223 in the first-line mCRPC setting trial, have made us somehow 'rediscover' the potential of radium-223 used early in the treatment sequence. Until now, the use of radium-223 was delayed to the third or fourth line—except for patients ineligible for any available systemic mCRPC treatment—(EMA, 2024c) given the increased risk of bone fractures shown by the ERA 223 trial (abiraterone acetate/-prednisone plus radium-223). After the recommendation of delaying its use in the treatment sequence and avoiding using it concomitantly with abiraterone acetate (EMA, 2018)—which was conveyed, although differentially in Europe and the US, to its prescribing information—its

Table 2
Ongoing real-world evidence studies with radium-223.

STUDY	TYPE	N	COUNTRY	RESULTS	CONCLUSION
ROTOR (Badrising et al., 2020)	Noninterventional, multicentre, prospective, observational registry evaluating clinical outcomes of radium−223 treatment in a non-study population.	300	Netherlands	• 74.1 % of patients pretreated with docetaxel and 80.5 % with abiraterone and/or enzalutamide. • 6-months SSE-free survival rate:83 %. • PFS and OS after a median follow-up of 13.2 months: 5.1 and 15.2 months, respectively.	The OS benefit and SSE delay with radium−223 remained consistent with the ALSYMPCA trial despite patients receiving treatment in 2nd or 3rd line.
BELFIGO (Seront et al., 2020)	Multicentre, single-arm, retrospective observational study evaluating the treatment pattern of mCRPC patients receiving radium−223 in Belgium.	164	Belgium	• 31 % of patients received 1–4 injections; 69 % completed 5–6 injections. • 55 % of patients received radium in 1st line, 30 % in the 2nd line. • 1st line therapy: 58 % abiraterone, 18 % docetaxel, and 16 % enzalutamide. • Median OS: 23.9 months with 5–6 injections vs 7.0 months with 1–4 injections.	This cohort achieved a higher median OS when completing 5–6 injections compared to 1–4 injections.
CAPRI (Kuppen et al., 2020)	An observational, multicentre cohort study of patients with mCRPC treated with radium−223	285	Netherlands	• Median OS with radium−223 was 23.8 months in the 1st line vs. 17.0 and 10.4 months in 2nd and 3rd line or later, respectively. • SSE-free survival was 12.5 months in the 1st line vs. 8.7 and 7.5 months in 2nd and 3rd line or later, respectively	This study highlights that earlier utilization of radium−223 may provide longer median overall survival compared to those receiving it in later lines
EPIX (George et al., 2022)	Retrospective cohort study of electronic health records in the U.S. Flatiron Database evaluating patient characteristics associated with survival of $\geq$ 2 years after radium−223 treatment for mCRPC.	1180	U.S.	• In patients who survived $\geq$ 2 vs $<$ 2 years, 47 % received radium−223 as a 1st line treatment vs. 26 % treated in later lines. • Patients who survived $\geq$ 2 years after starting radium−223 were younger and had better ECOG PS, lower disease burden, and less use of prior chemotherapy than those who survived $<$ 2 years.	This study reinforces that appropriate patient selection can be crucial for maximizing the survival benefit of radium−223.
PARABO (Palmedo et al., 2023)	Observational, prospective, single-arm cohort study designed to assess pain and bone pain–related QoL in patients with mCRPC receiving radium−223	354	Germany	• Clinically meaningful pain response in 59 % of evaluable patients. • Pain control reported in 67 % of patients. • Median OS: 17.2 months. It as was longer in patients who received 5–6 radium−223 injections than in those who received 1–4 injections.	In this large, contemporary, real-world study, radium−223 was proven to provide clinically meaningful pain reduction and OS benefits, particularly in those who had received 5–6 injections. The safety profile was consistent with that of the ALSYMPCA trial.
Galicina Study (Anido-Herranz et al., 2024)	Multicentre, retrospective study from 7 Galician medical centers in patients with mCRPC treated with radium−223 in 2nd, 3rd line or later.	143	Spain	• Median OS: 12 months; 17 months with radium−223 in the 2nd line, 11 months in the 3rd or further line, and 7.5 months in the 4th or further line. • A higher ALP level (>354 UI/L) was correlated with worse OS. • Patients who received the full 6 cycles of radium−223 had a better OS prognosis than patients who received less than 6 cycles.	This contemporary study in the EU reinforces the survival benefits of radium−223, which can be observed in each line of therapy for mCRPC. In addition, the ALP level was found to be an important prognostic factor in bone-dominant mCRPC.
RAPIT (Huang et al., 2024)	An observational study to assess safety and survival in patients suffering from castration-resistant prostate cancer (CRPC) which has spread to the bone and were treated with radium−223 in routine clinical practice	224	Taiwan	• Radium−223 was 1st or 2nd line therapy in 23.2 % and 47.7 % of patients, respectively. • Overall, 68.8 % of patients received 5–6 injections of radium−223: 84.3 % when used as 1st line therapy, 65.7 % when 2nd line and 64.1 % when 3rd or further line. • More chemotherapy-naïve patients (61.9 %) completed the 6-cycle radium−223 treatment vs. chemotherapy-exposed patients (56.7 %). • Median OS: 15.7 months, with patients receiving 5–6 radium−223 injections and earlier radium−223 use showing longer OS than those receiving fewer injections and later use.	Introducing radium−223 earlier in the treatment sequence is beneficial to patients with mCRPC, as it increases the likelihood patients will receive 5–6 cycles, which results in better survival outcomes than later use.

OS, overall survival; PFS, progression-free survival; QoL, quality of life; SSE, symptomatic skeletal events

Table 3
Ongoing clinical trials with radium-223.

Study / Design	N	Objectives	Start /end date	Inclusion Criteria	Interventions	Primary Outcomes	Secondary Outcomes
DORA (Morris et al., 2021) Phase 3, open-label, randomized.	738	To assess the efficacy of radium−223 and docetaxel vs. docetaxel alone in mCRPC	Jun 2018 / Dec 2024	mCRPC progression, ≥ 1 of the following: PSA progression, soft tissue, or bone, without visceral metastases.	Docetaxel (60 mg/m^2) + radium−223 (55 kBq/kg) vs. docetaxel (75 mg/m^2)	OS	Radiographic PFS, time to pain progression, quality of life.
RADIANT (Fizazi et al., 2021) Phase 4, randomized, open-label, multicenter	696	To compare the efficacy and safety of radium−223 vs. a second line of anti-hormone therapy	Nov 2020 / May 2025	Progression after first-line antihormonal therapy, ≥ 4 bone metastases, no significant visceral disease	Radium−223 (55 kBq/kg in 6 cycles) vs. second line of hormonal treatment.	OS	Time to first skeletal event, radiographic PFS, time to pain progression.
COMRADE (Shaya et al., 2021) Phase 1/2, randomized	133	To evaluate the combination of radium−223 and olaparib in patients with bone metastases from mCRPC	Oct 2018 / Nov 2023	Progressive disease, ≥ 2 bone metastases, no visceral metastases, no prior treatment with radium−223 or PARPi.	Radium−223 (55 kBq/kg, 6 cycles) + olaparib (Twice daily)	Maximum Tolerated Dose (MTD) and Radiographic Progression-Free Survival (rPFS)	PSA response, adverse events, OS.
Alphaβet (Kostos et al., 2022) Phase 1/2, prospective, single-arm	36	To evaluate the combination of radium−223 and ^{177}Lu-PSMA-I&T in mCRPC.	Sept 2022 / Dec 2026	2nd generation androgen receptor progression, ≥ 2 bone metastases, no discordant disease in FDG PET/CT	Dose escalation of ^{177}Lu-PSMA-I&T (7.4 GBq every 6 weeks) + radium−223 (27.5 or 55 kBq/kg every 6 weeks)	Dose-limiting toxicities, BAT, PSA_{50} response rate.	Radiographic PFS, OS, quality of life.

BAT, bipolar androgen therapy; FDG PET/TC, fluorodeoxyglucose-positron emission tomography computerized tomography; OS, overall survival; PARPi, Poly (ADP-ribose) polymerase inhibitor; PFS, progression-free survival; PSA, prostate-specific antigen.

therapeutic potential was significantly reduced as by this stage patients commonly present with visceral metastases, which are a contraindication for the use of radium-223.

Real-world clinical practice rarely mirrors the controlled conditions of clinical trials. Despite the lack of guidance for using radium-223 with either abiraterone acetate/prednisone or enzalutamide, several retrospective studies have shown that these combinations were not uncommon before the ERA 223 results were published (Sartor et al., 2019, Shore et al., 2020, McKay et al., 2021, Higano et al., 2023). One of these studies found that the use of BPA was lower than desired (67 % of these patients had received prior BPA and 55 % received concomitant BPA) (Shore et al., 2020). Notably, this use was greater than in the ERA 223 trial, where 41 % of patients were on BPA at study entry, and subsequent initiation of BPAs was not permitted (Smith et al., 2019). Conversely, in the PEACE-3 trial, ~50 % of patients were using BPA at the study entry, which later became mandatory for all patients precisely in the light of the ERA 223 results (Gillessen et al., 2024). The great reduction in the cumulative incidence of bone fractures observed when BPA was introduced as SoC strongly suggests that this could also have been the case in the ERA 223 trial if using a BPA had been mandatory. The results of the PEACE-3 trialrevisit the possibility of leveraging the benefits of radium-223 early in the treatment sequence, when patients still have asymptomatic or mildly symptomatic bone metastases and no known visceral metastases.

The results of the PEACE-3 trial and the treatment option offered by these findings deserve to be further discussed. The first results presented (ESMO 2024) showed a significant improvement in rPFS of the combination of enzalutamide plus radium-223 vs. enzalutamide alone (Gillessen et al., 2024). Although this endpoint does not measure clinical benefit, the OS difference between the two treatment groups, although still immature, was clinically meaningful. Given the increased risk of hypertension for enzalutamide (Zhu and Wu, 2019), patients were also likely to receive antihypertensive therapy. Therefore, most patients in the combination group received a quadruplet or quintuplet combination of enzalutamide, radium-223, BPA, ADT, and probably antihypertensive therapy. The available information is still scarce until the full results are published. However, the data presented indicate that the incidence of grade ≥ 3 hypertension was high in both treatment groups, as this was the most frequent TEAE (34 %) in the combination arm, and no TEAE ≥ grade 3 was increased by more than 5 % in the this arm vs. the enzalutamide alone arm (Gillessen et al., 2024).

Although these results support that radium-223 combined with an ARPI (in this case, enzalutamide) is effective and may be safe—provided preventive administration of a BPA is used—, it should be noted that since 2014, when this trial started, the current SoC has changed. As widely discussed in this review, the SoC in PC has evolved to include the early use of ARPIs (either for mHSPC or nmCRPC) rather than reserving them solely for mCRPC. This contrasts with the PEACE-3 trial, where the majority of patients received enzalutamide combined with radium-223 in the mCRPC setting, with only 2 % having had prior treatment with abiraterone acetate/prednisone or enzalutamide.

The results of this trial are theoretically applicable in countries where ADT alone remains the treatment for mHSPC patients (most cases progressing to mCRPC (Verry et al., 2022)). However, retrospective studies have shown that in clinical practice, many patients receive radium-223 not only with abiraterone acetate/prednisone or enzalutamide, but also after these treatments (Sartor et al., 2019, Shore et al., 2020, McKay et al., 2021, Higano et al., 2023). Given the lack of prospective trials, real-world experience can provide valuable insights into treatment patterns and outcomes.

Until the results of the PEACE-3 trial become fully available, some unanswered questions still make the applicability of the results uncertain. This includes the type and length of use of the BPA and safety issues. On-going trials with radium-223—especially DORA and RADIANT—will help to make the best of the benefit offered by radium-223 in the treatment of mCRPC and to define its place in the therapeutic sequence. Ongoing studies with other treatment alternatives will also contribute to shaping the treatment landscape in the near future.

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Declaration of Competing Interest

The authors declare the following financial interests/personal

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Authors' contributions

All authors participated in the conceptualization of the work, analyzing and interpreting data, drafting the first version of the manuscript, and critically reviewing the subsequent versions. All authors approved the final version of the manuscript before submission.

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Glossary

ADT: androgen deprivation therapy
AR: androgen receptor
ARPIs: androgen receptor pathway inhibitors
BPA: bone-protecting agents
CI: confidence interval
DDR: DNA damage repair
EMA: European Medicines Agency
FDA: Food and Drug Administration
HR: hazard ratio
HRR: homologous recombination repair
ibPFS: image-based progression-free survival
LHRH: luteinizing hormone-releasing hormone
mCRPC: metastatic castration-resistant prostate cancer
mHSPC: metastatic hormone-sensitive prostate cancer
nmCRPC: non-metastatic castration-resistant prostate cancer
OS: overall survival
PARPi: Poly (ADP-ribose) polymerase inhibitor
PC: prostate cancer
PSA: prostate-specific antigen
PSMA: prostate-specific membrane antigen
HRQoL: health-related quality of life
rPFS: radiographic progression-free survival
SSE: symptomatic skeletal events
SoC: standard of care

Alvaro Pinto, MD, PhD. Medical oncologist with experience in the field of prostate cancer, both from a research and a clinical practice perspective. Member of the Board of Directors of GUARD Consortium, a multidisciplinary cooperative group with the goal of improving and developing research projects in prostate cancer.

Mario Domínguez Esteban, MD, FEBU. Chief of the Uro-Oncology Section at Hospital Universitario Marqués de Valdecilla. He is specialized in Uro-Oncology and Minimally Invasive Surgery and has extensive clinical and research experience. He leads specialized units for prostate and bladder cancer at Hospital Universitario Marqués de Valdecilla, and his expertise spans robotic and laparoscopic surgery, laser prostate treatments, and renal transplantation. Actively involved in academic teaching, clinical trials, and scientific publications, he contributes to the advancement of uro-oncology through research, innovation, and professional training.

Alfonso Gomez-Iturriaga MD PhD. Medical specialist, expert in Radiation Oncology, with a special interest in prostate cancer—localized, locally advanced, and metastatic. He is the author of multiple publications and the principal investigator of projects related to his field of interest.

Alejo Rodriguez-Vida MD PhD. Medical Oncologist specialized in Genitourinary Cancers. He is coordinator of the Multidisciplinary Meeting in Genitourinary Tumours at Hospital del Mar and associate professor of Oncology at University Pompeu Fabra Barcelona.

Juan Antonio Vallejo Casas MD, PhD. Head of Nuclear Medicine Department. Chairman of the Endocrinology Working Group (SEMNIM). Ex-President of Spanish Society of Nuclear Medicine and Molecular Imaging. Expert in the field of Teragnosis and molecular imaging. PI in several clinical trials in Prostate and Thyroid cancer. Master in Health Economy and Management of health organizations. Master in Clinical Management.

Elena Castro. Medical Oncologist and researcher in prostate cancer at Hospital 12 de Octubre in Madrid, Spain. Her research interests span preclinical studies to clinical trials. Her work has addressed the clinical implications of genetic and genomic variants in prostate cancer. She has been involved in several clinical trials investigating new treatment strategies for patients with prostate cancer.