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REVIEW ARTICLE

Castration-resistant prostate cancer with bone metastases: toward the best therapeutic choice

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Abstract

The treatment landscape for metastatic castration-resistant prostate cancer has evolved extremely in recent years and several drug classes are now available. Nonetheless, the lack of validated predictive biomarkers makes therapeutic choice and the best sequential approach difficult. The location of the metastatic site could be a valid criterion for choosing among the treatment options available. Although bone remains the most frequent metastatic site and a possible target for many drugs, recent data suggest a profound shift in the disease spectrum with visceral metastases increasing incidence. This review describes the presently available and ongoing therapies for patients with CRPC and bone metastases, focusing on the role of bone metastases as a possible driver for selecting therapies in these patients.

Keywords Metastatic castration-resistant prostate cancer · Bone metastases · Chemotherapy · Androgen receptor signaling inhibitors · radium223 · Sipuleucel-T · ^{177}Lu-PSMA-617 · PARP inhibitors

Introduction

Prostate cancer (PC) is the second most diagnosed cancer among men worldwide, and in patients with metastatic PC, the prognosis is poor with a 5-year survival rate reaching 30% [1]. Docetaxel combined with prednisone has been the only therapeutic option for these patients for a long time; however, in recent years, the therapeutic scenario has been considerably enriched. In particular, androgen receptor signaling inhibitors (ARSIs), including abiraterone acetate and enzalutamide, the second generation taxane cabazitaxel, the immuno-modulatory agent sipuleucel-T, the radiopharmaceutical agents such as radium-223—for bone metastases—and ^{177}Lutetium-prostate-specific membrane antigen (PSMA)-617, and finally, the poly (ADP-ribose) polymerase (PARP) inhibitors, olaparib and rucaparib—for molecularly selected patients with mutations in DNA damage repair genes—are currently available. All these drugs were approved by regulatory agencies based on an improvement in overall survival (OS) [2–4]. Among the strategies detected to extend survival, the opportunity to act against bone metastases is a proof gained only in recent times. Although only 3% of patients have bone metastases at the diagnosis of PC, this percentage increases along the time and in metastatic castration-resistant prostate cancer (mCRPC) setting may arrive approximately to 90% [5]. The presence of bone disease is an important turning point in the management of mCRPC; effectively, bone metastases are virtually incurable and the skeletal-related events (SREs), including pathologic fracture and spinal cord compression, may be associated with significant morbidity and mortality, in addition to a general impairment of the quality of life (QoL) [5–7]. Several trials analyzed the prognostic role of bone metastases concluding that the volume of bone metastases and the intensity of the pain are the most important survival predictors [5, 7]. In this perspective, drugs targeting

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specifically bone metastases with different mechanisms of action, such as alpha emitting radiopharmaceuticals, zoledronic acid (ZA), and denosumab, have been developed [5, 7]. The aim of the present review is to discuss the role of bone disease in mCRPC and the impact of different drugs currently available in this setting, identifying therapy that may be the most appropriate, according to disease characteristics and patient's comorbidities.

Course of the disease according to the metastatic site

Although bone is still considered the main site of metastases in mCRPC, the prevalence of visceral disease is more frequent than in the past, probably also because of improvement in life expectancy deriving from the use of new available drugs [8, 9]. Generally, patients were identified in three different prognostic groups based on the metastatic site location: exclusively lymph nodes ≤ 25% of the cases), bone (90%), and visceral disease [10, 11]. Patients with the lymph nodes disease have a better prognosis compared to patients with visceral metastases. These trend have been confirmed by a retrospective analysis evaluating the baseline characteristics of 3993 mCRPC patients enrolled in several pivotal trials on mCRPC between 2000 and 2010 [12]. The percentages of patients with nodal, visceral (equally divided in lung and liver sites), and bone metastases were 5%, 16%, and 79%, respectively. Patients with nodal disease only had a longer survival (27 months) compared to patients with lung or liver disease (14 months), while patients with bone-only disease presented an intermediate life expectancy (20 months)[12]. A second study analyzed retrospectively 3857 patients included in the Surveillance, Epidemiology, and End Results (SEER) program Medicare insurance-linked database between 1991and 2009 [13]. Similarly, to the previous analysis, patients with exclusive nodal disease (2.8%) had the longest survival (range, 43–61 months), while patients with visceral disease had the worst prognosis. Patients with exclusive visceral disease (6.1%) at diagnosis had a life expectancy of 16–26 months compared to 14–19 months of the patients with visceral and bone (10.9%) disease [13]. Apart from these two opposing situations which concern a minority of patients with mCRPC (about 20%), the majority is represented by patients with only bone metastases (about 80%) (survival range, 24–32 months). A small part of these cases is characterized by concomitant, not prognostically relevant, lymph node disease [12]. The staggering persistent percentage of patients with only bone localizations leads to consider bone as the predominant clinical target in mCRPC.

Therapeutic opportunities for CRPC patients with bone metastases

Previous data indicated that bone disease should be evaluated as a persistent primary target for the treatment of PC to avoid, limit, or delay the morbidity and mortality rates deriving from possible bone-related events, such as pain, bone fractures, and spinal cord compression. Docetaxel, cabazitaxel ARSIs, radiometabolic therapies (radium-223 and ^{177}Lu-PSMA-617), sipuleucel-T, and PARP inhibitors demonstrated a benefit in randomized prospective clinical trials, even if in different settings of the mCRPC disease. Among these effective agents, some have been shown to increase survival without data regarding the pain palliation or skeletal events (SEs) prevention. We analyzed these results focused on those with available data on pain reduction and a delayed time to SRE. The increase in OS and the activity on SEs observed in the pivotal studies are reported in Table 1.

Agents only improving survival

Sipuleucel-T is a cancer vaccine that received Food and Drug Administration (FDA) approval in 2010 for the treatment of patients with asymptomatic or slightly symptomatic mCRPC regardless of the previous treatment line. In the pivotal phase III trial, IMPACT study, patients with visceral metastases and/or pathologic long-bone fractures, spinal cord compression, and with bone pain due to cancer have been excluded, while medical castration or bisphosphonate therapy was required at least until the time of disease progression [14]. The incidence of bone fractures and the time to the first SRE were not reported, while a greater survival benefit of 4.1 months and a 22% reduction of death risk was observed in the control arm vs placebo [15]. However, the survival benefit was proved for mCRPC patients with low disease burden, but has not been confirmed for patients with more advanced disease (> 20 detected bone lesions) [16, 17].

Agents improving survival and relieve bone pain

Docetaxel represents the only first-line chemotherapy for mCRPC approved based on the results of two-phase III trials. Both studies, TAX 327 and SWOG 9916, showed improvement of survival in patients treated with docetaxel (median OS, 19.2 and 17.5 months, respectively) compared to placebo or mitoxantrone plus prednisone agents [18, 19]. However, only TAX 327 reported the positive impact of docetaxel on pain palliation. Cabazitaxel, a new generation taxane, received the United State (US) and European regulatory agencies approval in 2011 for patients with

Table 1 Summary of efficacy of overall survival improving agents in mCRPC and skeletal outcomes

Agent	Abiraterone		Enzalutamide		Radium-223	Docetaxel		Cabazitaxel	Sipuleucel-T	^{177}Lu-PSMA 617	Olaparib
Trial (ref)	COU-AA-302 [25]	COU-AA-301 [24]	PREVAIL [23]	AFFIRM [27]	ALSYMPCA [51]	TAX-327 [18]	SWOG 9916 [19]	TROPIC [20]	IMPCT [14]	VISION [4]	PROfound [76]
Population	Asymptomatic/mildly symptomatic	All	Asymptomatic/ mildly symptomatic	All	Symptomatic bone metastases	All	All	All	Asymptomatic/ mildly symptomatic	All (PET-PSMA positive)	All (dDMR)
N of patients	1088	1195	1717	1119	922	1006	770	755	512	831	387
Setting	Chemo naïve mCRPC	Post docetaxel mCRPC	Chemo naïve mCRPC	Post docetaxel mCRPC	Pre e post docetaxel mCRPC	Chemo naive mCRPC	Chemo naive mCRPC	Post-docetaxel mCRPC	Chemo naïve mCRPC	Post ARSI and chemotherapy	Post ARSI
Control arm	Prednisone + placebo	Prednisone + placebo	Placebo	Placebo	Placebo and standard of care	Prednisone + placebo	Mitoxantrone + prednisone	Prednisone + placebo	Placebo	Soc	ARSI
OS vs control arm (mo)	NR vs 27.2	14.8 vs 10.9	32.4 vs 30.2	18.4 vs 13.6	14.9 vs 11.3	19.2 vs 16.3	17.5 vs 15.6	15.1 vs 12.7	25.8 vs 21.7	15.3 vs 11.3	17.5 vs 14.3
Reduction death risk	21%	26%	29%	37%	31%	24%	20%	30%	22%	38%	33%
Secondary endpoints correlated to bone disease	Times to opiate use for cancer-related pain	Time to first SRE Pain palliation rate	Time to first SRE	Time to first SRE	Time to SSEs	Pain reduction	NO	Pain response	NO	Time to SSEs	Time to pain progression

OS overall survival, *SRE* skeletal-related event, *SSEs* symptomatic skeletal events, *N* number, *ref* reference, *mCRPC* metastatic castration-resistant prostate cancer, *ARSI* androgen receptor signaling inhibitor

mCRPC previously treated with docetaxel. In the pivotal trial, TROPIC study, patients relapsed after first-line docetaxel (25% visceral and 84% bone metastases) were enrolled to receive cabazitaxel plus prednisone vs mitoxantrone plus prednisone [20]. Cabazitaxel showed to significantly improve OS compared to the control arm (15.1 vs 12.7 months, respectively) with a 30% reduction of the risk of death; only a slight reduction of grade 3 or higher pain compared with the control arm (1% vs 2%) has been reported. No data have been reported concerning a particular activity of docetaxel and cabazitaxel in reducing or delaying SEs [21, 22]. Therefore, chemotherapy represent an important choice for patients presenting with high volume disease, comprising mainly visceral metastases, but without a demonstrated benefit for patients with prevalent bone disease.

Agents delays or prevent SRE, relieve bone pain, and improving survival

Unlike previous agents, in the pivotal trials of both the novel hormonal agents, abiraterone acetate and enzalutamide, and the radiopharmaceutical radium-223, the evaluation of skeletal events and bone-related pain palliation are reported as secondary endpoints [23–27]. A summary of phase III studies that evaluated impact on SRE drugs is reported in Table 2

Abiraterone acetate combined with low-dose prednisone received the FDA approval for the treatment of patients with mCRPC previously treated with docetaxel based on COU-AA-301 trial [24]. Of 1195 enrolled patients, 90% displayed bone metastases. Abiraterone, compared to placebo, resulted in improving OS (14.8 vs 10.9 months, respectively), reducing risk of death of 35% and pain. Moreover, in a subsequent analysis, abiraterone was shown to also significantly delay the time to first SRE vs placebo (9.9 vs 4.9 months), although the incidence rate was similar in both treatment groups [28, 29]. A subsequent trial, COU-AA-302, enrolled 1088 mCRPC asymptomatic or pauci-symptomatic patients without visceral metastasis, led to FDA approval for patients before a docetaxel-based regimen. In this study median OS was increased to 3 years in chemotherapy-naïve patients treated with abiraterone and prednisone, compared with placebo [25]. No data regarding the delaying SRE are available, whereas a delay in the time to administration of opiates for pain palliation was reported. Enzalutamide was testing in 1199 mCRPC patients previously treated with 1 or 2 chemotherapy regimens (AFFIRM trial) and in chemotherapy-naïve patients (PREVAIL trial) [23, 27]. Conversely to COU-AA-302, PREVAIL trial included also patients with visceral metastases, representing about 12% of enrolled patients [24]. Enzalutamide improved OS compared to placebo (18.4 vs 13.6 months, respectively) reducing the time to prostate-specific antigen (PSA) progression, radiologic progression-free survival (rPFS), and time to first SRE, suggesting an impact on disease progression in bone [30]. Worthy of mention is that the drug turned out to be effective independent of the number of bone lesions (> 20 or not). Based on these results received the US and European regulatory agencies approval. In the CARD trial, patients previously treated with docetaxel and an ARSIs (abiraterone or enzalutamide) have been enrolled to receive cabazitaxel or the other ARSIs. PFS (primary

Table 2 Summary of phase III studies that evaluated impact on skeletal-related event

Agents	Abiraterone		Enzalutamide		Radium-223	
Trial	COU-AA-302 [24]	COU-AA301 [23]	PREVAIL [22]	AFFIRM [26]	ALSYMPCA [36]	
					Pre-chemo	Post-chemo
Bone disease	51%	89%	85%	92%	100%	
N of metastasis						
0	NR	R	15%	38%	0	
1–9	NR		53%		60%	
10–20	49%		16%		31%	
> 20			%	38%	9%	
superscan	NR			0%	0%	
Time to SER vs placebo (mo)	NR	20.3 vs 25.0	31.1 vs 31.3	13.3 vs 16.7	15.6 vs 9.8	
					7.8 vs 13.5	19.5 vs 17.0
Delay of SSE/SRE vs control (mo)	NR	4.7 (SRE)	0.2 (SRE)	3.4 (SRE)	5.8 (SSE)	
					3.7	2.5
HR benefit	NR	0.61	0.72	0.69	0.66	
					0.62	0.74

NR nor reported, *SRE* skeletal-related event, *SSE* symptomatic skeletal event, *HR* hazard ratio

endpoint) and OS (secondary endpoint) were higher in patients receiving cabazitaxel compared to ARSIs: 4.4 and 13.6 (hazard ratio [HR] 0.52; 95% CI 0.40 to 0.68; $p < 0.001$) vs 2.7, and 11.0 months (HR, 0.64; 95% CI 0.46 to 0.89; $p = 0.008$), respectively. Among the secondary endpoint, pain response was observed in the 45% of the patients treated with cabazitaxel and in the 19.3% of those receiving ARSIs; SEs occurred in the 18.6% and 27% of the patients treated with cabazitaxel or ARSIs, respectively, while the median time to a symptomatic SE was 16.7 months in the ARSIs group and not reached in the cabazitaxel group (HR, 0.59; 95% CI 0.35 to 1.01).

Radium-223 is a radionuclide emitting predominantly alfa particles, approved in 2013 by FDA for the treatment of mCRPC patients with symptomatic bone metastases and unknown visceral metastatic disease. Indeed, in the ALSYMPCA study, patients with visceral disease or lymphadenopathy greater than 3 cm were excluded [26, 27]. Compared with placebo, radium-223 significantly improved OS in these population (14.9 vs 11.3 months, respectively). Moreover, the time to first SRE was significantly prolonged (15.6 vs 9.8 months) and the QoL especially in the pain improved. Different radium-223 regimens have been investigated in patients with mCRPC (standard-dose: 55 kBq/kg every 4 weeks for six cycles; high-dose: 88 kBq/kg every 4 weeks for six cycles; extended-schedule arms: 55 kBq/kg every 4 weeks for 12 cycles). High-dose or extended-schedule regimens did not improve symptomatic skeletal event-free survival and were associated with more grade ≥ 3 TEAEs. Therefore, the standard-dose schedule remains the main option for patients with symptomatic mCRPC [31].

More recently, ^{177}Lu–PSMA-617, a beta-particles emitting radioligand, received FDA breakthrough therapy designations for mCRCP with PSMA-expressing cells. ^{177}Lu-PSMA-617 plus protocol permitted standard of care, excluding chemotherapy, immunotherapy, radium-223, and other investigational drugs) was compared with standard of care showing superiority in the primary end points, imaging-based PFS (8.7 vs. 3.4 months, respectively) and OS (15.3 vs. 11.3 months, respectively). Among secondary end points, median time to symptomatic SEs was longer for ^{177}Lu-PSMA-617 compared to control arm (11.5 vs 6.8 months; HR, 0.50) [4]. According to site of disease only, these data support the use of enzalutamide, abiraterone acetate, docetaxel, and ^{77}Lu-PSMA-617 in mCRPC patients regardless metastatic site, while radium-223 should be used only in patients without visceral disease and preferably with limited nodal involvement with a cut-off of 3 cm [10].

Bone health management

All patients with bone metastasis should receive treatment with bone-targeted agents (BTAs) to preserve bone health. However, in the ABITUDE trial, zoledronic acid (ZA) was administered only to 11.8% of patients in clinical practice [32]. In another real-world European study, the authors demonstrated that 74% of patients with bone metastases received a BTA and only 53% received treatment within 3 months of bone metastasis diagnosis [33]. Recently, however, results of a real-world Germany study (PROBone register study) indicate overall good adherence to current guideline recommendation, with most prostate cancer patients starting antiresorptive therapy within the first 3 months after diagnosis of bone metastasis [34]. First ZA and subsequently denosumab showed to reduce the incidence of SREs in CRPC patients with bone metastases becoming so the standard of care in addition to systemic treatments [35]. Compared with others bisphosphonates (clodronate or pamidronate), only ZA has improved SRE-free survival and median time to the first SRE [36]. Fizazi et al. showed that denosumab was better than ZA for SREs prevention median time to first on-study SRE was 20.7 months with denosumab compared with 17.1 months with ZA (HR 0.82, 95% CI 0.71–0.95; $p = 0.0002$ for non-inferiority; $p = 0.008$ for superiority) [37]. Moreover, denosumab also delayed the onset of moderate/severe pain compared with ZA (6.5 months vs. 4.7 months, $p < 0.001$) improving QoL. In chemotherapy-naïve mCRPC patients, a post hoc analysis of the COU-AA-302 trial demonstrated that the concomitant use of BTAs, compared with no BTAs use, significantly improved OS (HR 0.75; $p = 0.01$) and increased the time to Eastern Cooperative Oncology Group Performance Status deterioration (HR 0.75; $p < 0.001$) and time to opiates use for cancer-related pain (HR 0.80; $p = 0.036$) [38]. The post hoc analyses of the phase III ERA-223 trial evaluated the use of bisphosphonates or denosumab in chemotherapy-naïve mCRPC patients enrolled to receive radium-223 or placebo, in addition to abiraterone acetate and prednisone/prednisolone [39]. The incidence of fractures in the subgroup of patients who received BTAs at baseline was less than in patients bone-health-agents-naïve (15% vs 37% in the radium-223 arm and 7% vs 15% in the placebo arm, respectively). Median SEs-free survival was 22.3 months with radium-223 and abiraterone acetate and 26.0 months in the control arm. Fractures were recorded in the 29% and 11% of patients receiving combined therapy and placebo plus abiraterone acetate, respectively.

The PEACE III/EORTC 1333 randomized trial compared enzalutamide plus radium-223 vs enzalutamide alone in asymptomatic or mildly symptomatic men with mCRPC. In the safety analysis, patients were enrolled to receive or not co-treatment with bisphosphonates or denosumab. The cumulative risk of fracture at 13 months without BTAs was

higher (37.4% in combined therapy arm vs 12.4% in enzalutamide alone) than with BTAs (2.2% in combined arm vs 0% in enzalutamide arm) [40].

In the randomized controlled trial TRAPEZE, patients with mCRPC received docetaxel for six cycles and prednisolone with ZA, strontium-89 (a single dose after chemotherapy) or both [41]. Sr-89 improved clinical PFS including time to pain progression, SRE or death, while ZA improved SRE-free interval in the post-chemotherapy maintenance therapy. Neither agent affected OS (Sr-89, $p = 0.74$; ZA, $p = 0.91$). Finally, regarding BATs safety, Fizazi et al. reported a higher incidence of hypocalcemia and osteonecrosis of the jaw (ONJ) in patients treated with denosumab compared with ZA (12.8% vs 5.8% and 2.3% vs 1.3%, respectively), although the difference was not significant for ONJ ($p = 0.09$) [37]. In the COU-AA-302, the safety profile was similar in both groups and ONJ was reported in < 3% of patients [38]. However, must consider that contrarywise to ZA that required dose adjustment based on glomerular filtration rate (eGFR) and is not recommended in case of eGFR < 30 mg/min/1.7 denosumab does not require dose adjustment in renal failure [42].

External beam radiation

Pain related to bone metastases may be effectively treated with radiation therapy. External beam radiation techniques (EBRT), including stereotactic body radiation therapy (SBRT), have had success for localized pain caused by bone metastases. Regarding EBRT, the results of studies comparing the single fraction of radiation (most commonly administered as an 8 Gy fraction) vs higher doses showed the same efficacy in many patients [43–46]. However, although EBRT is effective to treat painful bone metastases, with the conventional techniques, the amount of dose that can be delivered is limited by surrounding normal tissue. SBRT is a type of treatment that delivers extremely precise, very intense doses of radiation to cancer cells while minimizing damage to healthy tissue (*i.e.*, the spinal cord). SBRT demonstrated high local control rates when used to treat the spine, although it is associated with a higher risk of vertebral compression fracture [47]. Recently, Shulman et al. showed that EBRT administered to patients with prostate, lung, and breast cancer with asymptomatic bone metastases was associated with an increase in time to the first occurrence of either pain or an SRE (25 months for the untreated patients and 81 months for the patients receiving EBRT: $p < 0.001$). They concluded that EBRT should be considered in future trials on patients with asymptomatic bone metastases as it might have a role in the treatment of bone metastases before they produce pain or other SREs [48].

Predictor and prognostic factors in bone metastatic mCRPC

In daily clinical practice, patients presenting with mCRPC and bone metastases represent a very heterogeneous group. The presence of other site of metastases (nodes and viscera) in patients with bone disease may be an important driver to choose the most appropriate drug, as stated above. However, other variables, such as tumor burden, the presence of symptoms, concomitant medications and patient's comorbidities should be considered in planning a therapeutic strategy that is as personalized as possible.

Bone tumor burden

Patients enrolled in the four trials testing the two novel hormonal agents presented a limited bone disease, with the exception of the AFFIRM study in which 38% of the enrolled patients presented with more than 20 bone metastatic sites [23, 26]. In the radium-223 phase III study, 40% of patients carried out more than 20 bone metastatic sites, including approximately 9% of patients with a "superscan," and a correlation was shown between extension of bone disease and survival. This exploratory sub-analysis showed the possibility of an increased treatment benefit for patients with more than 6 bone lesions [26] (Table 2).

Symptoms

The presence of symptoms is both a relevant prognostic factor and an ethical issue in oncology. In TAX 327 study, which evaluated the efficacy of docetaxel in 1006 mCRPC patients, cases with symptomatic disease had a lower life expectancy than the asymptomatic ones [27, 49]. A possible explanation of this negative prognosis may be investigated with the obvious increased burden of disease in symptomatic patients [49, 50]. Studies with the ARSIs included both asymptomatic and symptomatic patients in the post-docetaxel setting, and AFFIRM trial presented the highest percentage of symptomatic cases (38%). On the other hand, only asymptomatic or mildly symptomatic cases were enrolled in the chemo-naïve setting [23–25, 51, 52], while in the ALSYMPCA study, only symptomatic patients were enrolled, and it is well known that symptomatic patients for pain are related with the poorest prognosis than the asymptomatic [26, 52] (Table 1).

Androgen receptor splice variant 7

During the past decade, the lack of new effective therapies to improve survival in mCRPC was associated with the

absence of efficacy markers. The androgen receptor splice variant 7 (AR-V7), a splice variant of the androgen receptor mRNA resulting in the truncation of the ligand-binding domain, has emerged as a biomarker for resistance to ARSIs [53]. AR-V7 expression in circulating tumor cells (CTCs) has been associated with poor outcomes in patients treated with second- and third-line hormonal therapy. In details, efficacy of abiraterone acetate and enzalutamide may be limited by a pre-existing AR mutation at baseline and during the natural history of the disease due to an adaptive and progressive clonal selection of the prostatic cancer cell clones exposed to these agents [53]. This innovative model could also explain the results of several retrospective data reporting a substantial cross-resistance with the sequential use of abiraterone acetate and enzalutamide and vice versa [54, 55]. The possible influence of the AR-V7 splice variant status in patients receiving radium-223 or taxanes is almost unknown. However, because of the different mechanism of action not involving the AR, the efficacy of radium-223 and taxanes may be not influenced by the AR status nor induce an adaptive negative selection responsible for a cross-resistance with abiraterone acetate and enzalutamide. In fact, several data seem to confirm the activity of taxane agents independently of the AR-V7 status [56, 57]. Recently, data regarding the predictive role of the AR-V7 status have been confirmed in a multicenter, prospective-blinded trial (PROPHECY) [58]. In this study, detection of AR-V7 in CTCs is independently associated with shorter PFS and OS in patients with high-risk mCRPC receiving abiraterone acetate or enzalutamide. These evidence allow to identify a priori the best treatment approach, especially in case of sequential treatment where the problem of an induced adaptive resistance may be more relevant. However, must consider that AR variants do not manifest in isolation, but rather are part of a complex, heterogeneous and ever-changing mCRPC genome and phenotype. To overcome the limitation of available clinically validated test (AdnaTest mRNA or Epic nuclear protein assays), the development of a broader resistance assays could be needed.

Treatment approach focusing on patient's characteristics

Abiraterone acetate, enzalutamide, and radium-223 are characterized by a good safety profile with no significant contraindications for their use in patients with mCRPC, even if presenting with relevant comorbidities. Abiraterone acetate is associated with some adverse events related to increased mineral corticoid levels due to CYP17 blockade, hypertension, hypokalaemia, and fluid retention, and a consequent slightly increased risk of developing arrhythmias, and cardiac failure, also cases of hepatotoxicity have been described [59] The concomitant use of low-dose corticosteroids, required to suppress adrenocorticotropic hormone (ACTH) drive, reduces the entity of these adverse events but may induce hyperglycaemia and reduction of bone density. A food-intake effect is also described, and then abiraterone acetate administration must be done in a fasting status. About enzalutamide seizures are a possible side effect, while for a potential risk of additive myelosuppression, radium-223 does not recommend concomitant with chemotherapy and, due to its fecal excretion, radium-223 should be administered only after a careful benefit-risk assessment in patients with acute inflammatory bowel disease, Crohn's disease, and ulcerative colitis. Moreover, due to the increased frequency of bone fractures, the combination of radium-223 with abiraterone acetate is not recommended.

Discussion

The heterogeneity of the disease in patients affected by mCRPC leads to several possible therapeutic choices varying from the simple "watch and wait" to interventional approach with different agents [21]. A possible treatment algorithm based on a comprehensive evaluation of metastatic site locations, burden of the disease, presence of symptoms and clinical setting is drafted in Fig. 1.

According to available data, in select patients with no-bulky solely lymph node metastasis, mainly not candidates to receive therapy choice (ARSIs), a simple watchful observation or focal treatments may be suggested, since as previously reported present a better prognostic profile [11, 12]. Conversely, patients with visceral metastases may benefit from a chemotherapy-based approach or ARSIs according to available data in different clinical settings.

As bone disease remains the most common clinical situation in mCRPC drugs acting bone metastases represent an important therapeutic opportunity in these patients. Currently, chemotherapy (docetaxel, cabazitaxel), ARSIs (abiraterone acetate, enzalutamide), and recently ^{177}Lu-PSMA-617 and PARPi are recommended for patients with disease spread to bone and/or visceral and/or (bulky) nodes.

With regard to patients with bone disease and lymphadenopathy less than 3 cm, all the available agents, including radium-223 and sipuleucel-T, may be prescribed, and therefore, the therapeutic choice could be identified keeping in account other clinical aspects such as age, general conditions, comorbidities, and the presence of symptoms. Moreover, the therapeutic scenario could be personalized in according to symptoms and history of the disease evaluated by PSA doubling time (PSA-DT). In fact, in an oligosymptomatic patient with a slow PSA-DT, a simple watchful observation may be a possible approach, whereas, in an oligosymptomatic patient with an increased PSA-DT, or an

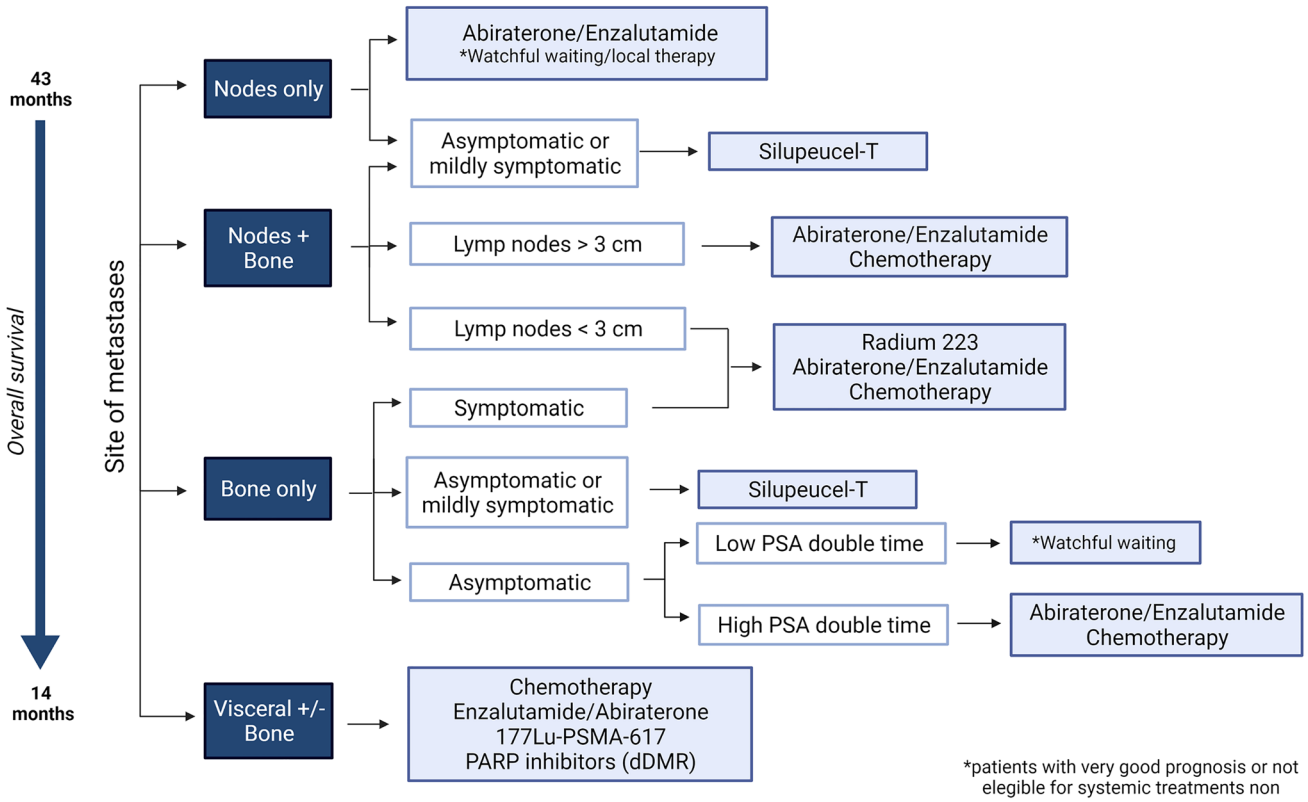

Fig. 1 Possible treatment algorithm in mCRPC based on metastatic site locations, presence of symptoms and clinical setting. *Created with BioRender.com*

evident progressive disease, ARSIs may be administrated as first choice. Sipuleucel-T is an alternative for asymptomatic or slightly symptomatic patients who have already received chemotherapy and ARSI.

Finally, in the symptomatic patient with only bone metastases in the post-chemotherapy setting, each one of enzalutamide, radium-223, cabazitaxel, and abiraterone acetate may be a good treatment choice. However, the most relevant data about symptomatic patients derive from the ALSYMPCA trial (100% of patients are symptomatic). In the AFFIRM trial, 28.3% of enrolled patients present a Brief Pain Inventory ≥ 4, while in the COU-AA-301 study, the symptomatic patients are 44%.

Current evidence indicates a consistent risk of cross-resistance between the ARSIs and suggest a possible use of docetaxel or radium-223 in direct sequencing to abiraterone acetate or enzalutamide; anyhow, the best sequential approach remains to be established.

Although the role of ARSI in the first-line treatment of mCRPC with bone metastasis remains the main one, a greater understanding of the molecular underpinnings of bone metastasis has contributed to an expansion of potential therapies in this setting. The mutation/amplification/upregulation of several receptor tyrosine kinases (TK) have been implicated in the development, growth, and progression of PC [60]. The vascular endothelial growth factor (VEGF) pathway is closely correlated with tumor proliferation, migration, and differentiation, and VEGF receptor signaling on osteoblasts and osteoclasts seems involved in bone formation and remodeling. Similarly, MET receptor, promoter to tumor growth and metastasis is expressed on osteoblasts and osteoclasts where, through a autocrine and paracrine mechanisms, regulates their activity and survival [61].

Dovitinib, a tyrosine kinase inhibitor (TKI) that binds fibroblast growth factor receptor 3, shown to improve bone scans and reduce SREs in the 26% of patients in a proof-of-principle study [62] and its efficacy has been investigation in combination with abiraterone (NCT01994590).

In a phase I trial, dasatinib, another TKIs, shown a reduction of disease progression and bone lesions of 57% and 30%, in mCRPC patients [63] subsequently confirmed in a phase II study with dasatinib in monotherapy. Nevertheless, a recent phase III trial testing dasatinib plus docetaxel vs docetaxel and placebo failed to provide a survival benefit [64], although a slight, but not significant delay in time to first SRE was observed in the experimental arm compared with the control arm. According to data suggesting a role for Src kinases in bone-related pathogenesis, dasatinib could

have affect bone in concomitance of docetaxel, although the difference in the time to first SRE delay with dasatinib vs placebo was not reported in a post hoc analysis [64, 65]. However, as dasatinib seems to exacerbate prostate tumor-induced osteogenesis, a combination with abiraterone/prednisone prior to chemotherapy is currently being investigated [66].

In the COMET-1 trial, cabozantinib failed primary endpoint of increasing OS in patients who had previously received docetaxel and abiraterone [67] achieving, however, secondary outcomes including bone scan response (BSR), radiologic PFS, SREs, CTCs, and bone biomarkers (bone alkaline phosphatase: BAP) reduction. These data agreed with the results of a randomized phase II study in which cabozantinib improved PFS and bone scans response with complete resolution in 12% of mCRPC patients [68, 69]. Because of its success emerged by ALSYMPCA trial, several studies investigated the efficacy of radium-223 with other therapies such as ARSIs or docetaxel. In the ERA 223 trial, the combination between radium-223 and abiraterone acetate in mCRPC failed to achieve the primary endpoint (symptomatic SE-free survival) showing an increase of the risk of fracture [39]. Therefore, the FDA and European Medicine Agency advised against this combination as first-line therapy for CRPC with bone metastases [70]. The updated analysis of the PEACE III trial confirms that in the absence of BTA, the risk of fracture is increased when radium-223 is added to enzalutamide, whereas, the risk remains almost abolished, in both arms, with preventive continuous administration of BTAs [71]. A randomized phase II study evaluated the addition of radium 223 to docetaxel in chemotherapy-naïve patients with CRPC and at least 2 bone metastases [72]. The combination was associated with longer-lasting decreases in serum tumor markers (PSA and BAP). Further data could come from the DORA study which is testing docetaxel given every 3 weeks vs docetaxel every 6 weeks plus radium-223 [73].

Finally, although in the pivotal trials, the role of poly ADP-ribose polymerase (PARP) inhibitors on bone health has not been investigated, these appear to play a critical role on mesenchymal stem cell (MSC)-driven osteogenesis in addition to providing an advantage in PFS and OS in CRPC patients with damage DNA mismatch repair [74]. Indeed, preclinical studies showed that PARP inhibitors have the potential to impede bone metabolism delaying and suppressing the MSC osteogenic differentiation, making them a promising option for treatment in CRPC with bone metastasis [74]. Combination therapies with olaparib and radium-223 in patients with mCRPC with known bone metastasis are currently under evaluation [75]. Ongoing clinical trials for bone metastatic CRPC are reported in Table 3.

Conclusion

Significant progress has been made in the development of therapies for patients with mCRPC in recent years. The bone site, mainly involved in these patients, may represent an important driver for treatment choice in patients with mCRPC, and therefore, the knowledge on how to make the best use of available agents is required. Recently, the commitment of the scientific community has focused on possible combinations between new hormonal agents and radium-223 or the use of new agents (poly PARP inhibitors, TKI, immune checkpoints inhibitors) to reach new goals in terms of survival in patients with bone disease. Pending such results, the objective is to maximize the clinical benefits deriving from the current drugs, identifying the suitable patient for each therapy, and planning accurately sequences to limit the developing of awaited treatment resistance. In the meanwhile, on the wake of the extremely positive survival results, un-hoped just few years ago in the field of mCRPC, we deem that the present analysis of data provides some useful information for a more precise and rewarding use of the present agents in the mCRPC scenario.

Table 3 Recruiting and active not recruiting phase II/III clinical trials with bone-related endpoints mCRPC

Clinical trial	Phase	Status	N of patients	Drugs	Primary endopoint	Bone-related secondary endpoint
NCT03230734	II	Recruiting	70	Radium-223 + Docetaxel + Prednisone	HRQoL	NA
NCT02346526	II	Active not recruiting	22	Radium-223	Change from baseline in bone scan index at 2 months	Mean percent change in bone scan lesion area by 18 months survival status Bone turnover markers
NCT03317392	II	Recruiting	120	Olaparib + Radium-223	rPFS	Symptomatic skeletal event
NCT03458559	III	Active, not recruiting	402	Rhenium-188-HEDP vs Radium-223	OS	Time to first SRE Effect on pain
NCT02043678	III	Active, not recruiting	806	Radium-223 + Abiraterone Acetate + Prednisone/Prednisolone	SSE-FS	Time to pain progression Time to opiate use for cancer pain
NCT02194842	III	Recruiting	560	Radium-223 + Enzalutamide	rPFS	First symptomatic SE Time and incidence of first skeletal progression-free Pain and time to pain progression QoL
NCT04616547	II	Recruiting	25	Tin Sn 117 m Pentetate	Sustained pain response	Time to first SSE Overall pain response rate and duration
NCT03305224	II	Active, not recruiting	10	Radium-223 + Enzalutamide	Changes ALP	Evaluation for bone metastasis by 18F-NaF-PET and scintigraphy Time to occurrence of SSEs Changes from baseline for brief pain inventory (BPI)
NCT03751436	II	Recruiting	39	Enzalutamide + Venetoclax (ABT-199)	PFS	Time to first SRE
NCT03344211	II	Recruiting	36	Enzalutamide ± Radium223	Changes in prostate cancer bone involvement	NA

mCRPC Metastatic castration-resistant prostate cancer, *HRQoL* health-related quality of life, rPFS radiographic progression-free survival, *OS* overall survival, *SSE-FS* symptomatic skeletal event-free survival, *PSA* prostate-specific antigen, *AE* adverse event, *ALP* alkaline phosphatase, *N* number, *HER* human epidermal growth factor receptor, *NA* not applicable

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Declarations

Conflict of interest No author declares any conflict of interest.

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