

# Targeting Bone Metastases in Metastatic Castration-Resistant Prostate Cancer

Joelle El-Amm<sup>1</sup> and Jeanny B. Aragon-Ching<sup>2</sup>

<sup>1</sup>The Lebanese American University, Department of Hematology and Oncology, Division of Internal Medicine, Beirut, Lebanon. <sup>2</sup>Clinical Program Director of Genitourinary Cancers, Inova Dwight and Martha Schar Cancer Institute, Fairfax, VA, USA.

## Supplementary Issue: Key Difficulties Associated with Cancer Biology

**ABSTRACT:** Skeletal involvement in metastatic castrate-resistant prostate cancer (mCRPC) is common and results in significant morbidity and mortality. The interaction of prostate cancer with the bone microenvironment contributes to progression of cancer in the bone leading to skeletal-related events (SREs). Studies aimed at targeting the bone have been carried out over the recent years. Bisphosphonates are synthetic pyrophosphate analogs first investigated for their role in SRE prevention with zoledronic acid as the main bisphosphonate that is approved by the US Food and Drug Administration for retardation of skeletal events in men with metastatic prostate cancer. Denosumab is another bone-targeted agent against uncontrolled osteolysis and serves as a RANK ligand inhibitor, superior to zoledronic acid in delaying SREs. Radiopharmaceuticals have played a role in targeting the bone microenvironment mainly in pain palliation in mCRPC utilizing strontium or samarium in the remote past, but only radium-223 is the first radiopharmaceutical that has yielded improvement in overall survival. The combination and sequencing strategies of these agents is the subject of multiple ongoing trials to guide the best use of these emerging agents.

**KEYWORDS:** bisphosphonates, zoledronic acid, denosumab, radium-223 radiopharmaceuticals, bone metastases, skeletal-related events, prostate cancer

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**CORRESPONDENCE:** Jeanny.Aragon-Ching@inova.org

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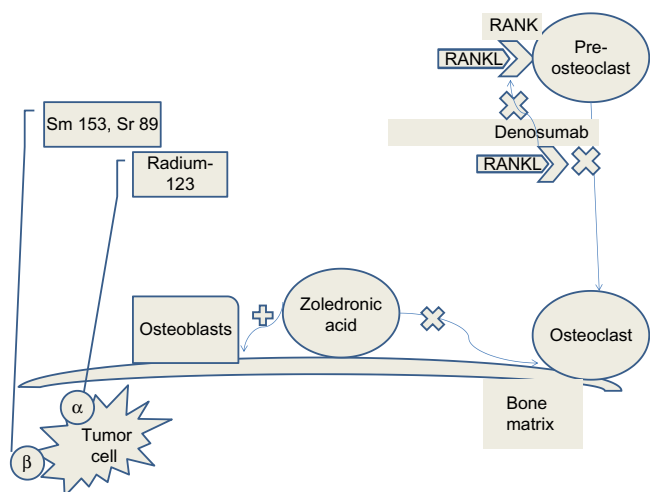
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## Introduction

Prostate cancer is the most common noncutaneous malignancy in the USA, and its prevalence is expected to increase with the increasingly aging population.<sup>1</sup> Most patients manifest with localized disease at presentation, although some will have disseminated disease or develop advanced disease with time.<sup>2,3</sup> Androgen deprivation therapy (ADT) has been the mainstay of therapy in metastatic prostate cancer, but despite an initial response to hormonal therapy, progression typically occurs within one to three years leading to a castration-resistant state.<sup>4</sup> The vast majority of metastatic castrate-resistant prostate cancer (mCRPC) develops bone metastases historically resulting in a significant increase in mortality and morbidity.<sup>5,6</sup> Morbidity due to bone metastases stems from the decline in the quality of life due to the increased risk of fracture, bone pain, and decreased hematopoiesis resulting in anemia as well as malignant hypercalcemia.<sup>7,8</sup> Skeletal-related events (SREs) have long been established as a valid end point in clinical trials

utilizing bone-targeted therapies. SREs include pathological fractures, spinal cord compression, and need for surgery and/or radiation therapy. Bone metastases not only affect the quality of life, but they have also been associated with detriment in overall survival (OS).<sup>9–12</sup>

Although bone metastases in prostate cancer appear osteoblastic on imaging, there is a role for both osteoblasts and osteoclasts in bone metastasis, leading to both increased bone formation and bone resorption, which opens the door to multiple mechanisms of action to target the bone microenvironment (see Fig. 1 for selected bone-targeted agents and their proposed mechanisms of action).<sup>13,14</sup> In addition, the complex interplay of osteoblasts, bone lining cells, osteocytes, and osteoclasts along with local and systemic factors and cytokines all influence the bone remodeling process. There are several growth factors involved in prostate cancer metastases, with proliferation via the endothelin-A receptor, bone morphogenic proteins, fibroblast growth factor, and use of markers for



**Figure 1.** Selected bone-targeted therapies in mCRPC and their mechanisms of action. Zoledronic acid binds to the bone matrix, preventing the activity of osteoclasts and stimulating osteoblasts. Denosumab binds to RANKL, preventing the binding of RANKL to RANK, thus inhibiting the activation of osteoclasts. Radiopharmaceuticals emit alpha- or beta-ionizing radiation to the tumor cell in the bone. Figure adapted from El-Amm et al.<sup>18</sup>

bone remodeling such as urine telopeptides, which have been used but not widely adopted in routine practice.

Docetaxel was the first agent approved by the US Food and Drug Administration (US FDA) in 2004 to combat mCRPC and became the standard first-line chemotherapy agent after showing both an improved OS and improved quality of life and decreased pain compared to placebo.<sup>15,16</sup> Since 2010, five new agents have been approved by the US FDA, namely, the CYP17 lyase inhibitor abiraterone

acetate, the antiandrogen enzalutamide, the T-cell activator sipuleucel-T, the microtubule stabilizer cabazitaxel, and the radiopharmaceutical radium-223.<sup>17,18</sup> Given the emergence of these new agents and the increased use of bone-targeted therapies (bisphosphonates and denosumab) in standard practice, the rate of reported SREs has been steadily declining.<sup>19</sup> This review will describe the bone-targeted therapies in mCRPC (see Table 1) and provide insight into their current and future use.

### Bisphosphonates

Bisphosphonates are nitrogen-containing compounds that adhere to hydroxyapatite in the bone with selective inhibition of farnesyl pyrophosphate synthase in areas of active remodeling stimulating osteoblasts and inhibiting osteoclast differentiation and survival.<sup>20,21</sup> Although many bisphosphonates have been studied, zoledronic acid remains the most commonly used bisphosphonate that was approved by the US FDA in 2002 to prevent SREs in men with metastatic prostate cancer after the failure of hormonal therapy. The trial that led to the approval of zoledronic acid by the US FDA in 2002 was based on a phase 3, randomized, placebo-controlled study. This trial enrolled 643 asymptomatic mCRPC patients who were randomized to receive 22 cycles of two different doses of intravenous (IV) zoledronic acid (either 4 mg or 8 mg) versus placebo every three weeks.<sup>22</sup> However, the dose was later switched to remain at 4 mg for all participants midway through the study due to concerns regarding renal impairment that was noticeable in the high-dose group. The primary end point of the study was the proportion of patients developing SREs, and the study met the trial end point with the zoledronic acid arm developing fewer

**Table 1.** Selected US FDA-approved bone-targeted agents utilized in mCRPC.

	ZOLEDRONIC ACID	DENOSUMAB	SR-89	SM 153	RADIUM 223
Agent class	Bisphosphonate	Monoclonal anti-body against RANK-L	Pure Beta-emitter radiopharmaceutical	Beta and Gamma-emitter radiopharmaceutical	Alpha-emitter
Route	Intravenous	Subcutaneous	Intravenous	Intravenous	Intravenous
Half-life (days)	6	25.4	50	1.9	11.4
Dosing frequency	4 mg IV every 3–4 weeks	120 mg SC every 4 weeks	1.5–2.2 MBq/kg, 40–60 μCi/kg body weight	1.0 mCi/kg IV	50 kBq/kg IV every 4 weeks
Efficacy	Significant decrease and delay in SREs and bone pain	Significant delay in SREs	Significant decrease in bone pain	Significant decrease in bone pain	Significant increase in OS, delay in SREs
Major adverse effects	Infusion reaction, hypocalcemia, osteonecrosis of the jaw	Hypocalcemia, osteonecrosis of the jaw	Myelosuppression	Myelosuppression	Gastrointestinal symptoms
FDA Approval	FDA approved 2002	FDA approved 2010	FDA approved 1993	FDA approved 1997	FDA approved 2013
Indication	Prevention of SREs in mCRPC with bone metastases	Prevention of SREs in mCRPC with bone metastases	Reduction of pain in mCRPC with bone metastases	Reduction of pain in mCRPC with bone metastases	mCRPC with bone metastases in the absence of visceral metastases



events with SREs (44.2% versus 33.2% for placebo;  $P = 0.021$ ). However, no significant differences in outcomes as far as OS, disease progression, performance status, or quality of life were observed, all of which were secondary end points. Treatment was initially planned for 15 months, but later, there was an extension phase at 24 months.<sup>23</sup> In the extension phase, zoledronic acid decreased the risk of SREs by 36% (relative risk = 0.64,  $P = 0.002$ ), delayed the time to first SRE by 167 days (488 versus 321 days;  $P = 0.009$ ), and even resulted in decreased bone pain compared to placebo. In patients receiving zoledronic acid, markers of bone resorption including the urinary N-telopeptide (uNTx) of type I collagen to urine creatinine ratio decreased steeply after one month (70%; 95% confidence interval [CI], 72.6–66.3). Serum bone alkaline phosphatase increased more in patients receiving placebo (+33.7%; 95% CI, 21.1–56.3).

Other bisphosphonates were also studied for the prevention of SREs in mCRPC, but none had obtained the approval of the US FDA. Pamidronate is a less potent bisphosphonate compared to zoledronic acid, and two randomized, placebo-controlled trials looking at the utility of pamidronate in reducing SREs in symptomatic mCRPC patients showed failure to meet the primary end point.<sup>24</sup> Another bisphosphonate that was studied is oral clodronate. One study failed to demonstrate pain relief in mCRPC to the bones, whereas another trial showed a trend toward improved bone progression-free survival with the use of clodronate, but the difference did not reach statistical significance.<sup>25,26</sup> A long-term follow-up of the trial showed that OS significantly favored the clodronate arm hinting to the possible antineoplastic role of the drug. Clodronate is the only bisphosphonate to date to have shown OS benefit,<sup>27,28</sup> although it had not gained the approval of the US FDA nor translated into routine adoption in clinical practice for the retardation of SREs.

Recently, the frequency of bisphosphonate administration has also been challenged. A study that included 1822 patients with breast cancer, multiple myeloma, or prostate cancer compared the outcomes of patients who received zoledronic acid either every 4 weeks or every 12 weeks and showed that there was no significant difference between the two arms for the primary end point, with 29% of patients in both the 4-week arm and the 12-week arm experiencing at least one SRE ( $P = 0.79$ ).<sup>29</sup> No significant differences were found between the two arms for time to first SRE ( $P = 0.60$ ), skeletal morbidity rate ( $P = 0.75$ ), pain scores ( $P = 0.75$ ), or Eastern Cooperative Oncology Group performance status (ECOG PS;  $P = 0.64$ ). Therefore, the optimal duration of bisphosphonate use, in light for potential long-term toxicity, has yet to be redefined.

Bisphosphonates as a class are generally well tolerated. The most common side effects include flu-like symptoms, mainly during the first infusion occurring in about half of the treated patients. Hypocalcemia occurs in ~6% of patients, and one of the most concerning side effects is osteonecrosis of the jaw (ONJ) that occurs in ~1% of patients, especially with long-term use, and in patients with other risk factors

such as those who have poor baseline dental hygiene, dental extractions, concomitant use of corticosteroids, or systemic diseases.<sup>30</sup> A major limitation of bisphosphonates is their nephrotoxicity that mandates careful monitoring and necessitates dose adjustment or even withholding the drug, in cases of renal impairment.

## Denosumab

Maintaining bone integrity requires a balance between production of bone by osteoblasts and resorption of the matrix by osteoclasts.<sup>31</sup> The receptor activator of NF kappa B (RANKL) is a member of the Tumor necrosis factor (TNF) family expressed on osteoblastic surface, and its receptor RANK is expressed by osteoclasts.<sup>32,33</sup> An important mechanism that leads to osteoclast formation, activation, adherence, and survival is the binding of RANK to its ligand (RANKL).<sup>34</sup> Denosumab is a fully human monoclonal antibody against RANKL mediating the inhibition of osteoclastic activity and is administered subcutaneously. An open-label, randomized, multicenter phase II trial reported in 2009 included prostate cancer patients among other malignancies.<sup>35</sup> This trial enrolled 111 asymptomatic metastatic prostate cancer patients who exhibited uNTx levels higher than 50 nmol/L bone collagen equivalents/mM creatinine and presence of more than one bone metastasis. Fewer patients receiving denosumab experienced SREs than those receiving bisphosphonates. To further determine the effects of denosumab on bone mineral density (BMD) and fractures in men receiving ADT for prostate cancer, a randomized, double-blinded, multicenter study, known as the HALT prostate cancer trial, looked at the primary end point of percent change in BMD at the lumbar spine at 24 months in men who were assigned to receive denosumab at a dose commonly used for osteoporosis at 60 mg subcutaneously every six months versus placebo.<sup>36</sup> At 24 months, the study met its primary end point of increasing BMD in the femoral neck, lumbar spine, and hip, along with lesser incidence of fractures in nonmetastatic prostate cancer patients receiving ADT. This trial helped in the later approval by the US FDA in 2011 of the use of denosumab for men with nonmetastatic prostate cancer receiving ADT who are at high risk for developing fractures to improve bone density mass. Another phase III, randomized, double-blind trial compared denosumab and zoledronic acid for the prevention of SREs in men with mCRPC.<sup>37</sup> A total of 1904 patients were randomized to receive either 4-mg zoledronic acid intravenously or 120-mg denosumab subcutaneously every four weeks. The primary end point was time to first on-study SREs. Denosumab delayed the time to first on-study SRE by 18% (20.7 versus 17.1 months; hazard ratio [HR]: 0.82; 95% CI, 0.71–0.95;  $P = 0.0002$  for noninferiority and  $P = 0.008$  for superiority). An on-study SRE did not require cessation of study treatment. Multiple-event analysis showed that denosumab delayed time to first and subsequent SREs (rate ratio: 0.82; 95% CI, 0.71–0.94;  $P = 0.008$ ). Survival and time to disease



progression were similar in both groups. The side-effect profile between both drugs was similar, although hypocalcemia events were noticeably more in the denosumab group compared to the zoledronic acid group, occurring at 13% versus 6% ( $P < 0.0001$ ), while ONJ occurred at a similar frequency in both groups although later follow-ups would show slight increase in cumulative effects. This trial garnered denosumab's label by the US FDA for the indication of prevention of SREs in men with metastatic prostate cancer.

The safety of long-term use of denosumab was recently reported.<sup>38</sup> The analysis of the open-label extension phase of the phase III trial showed no new long-term safety signals among patients who received denosumab initially or those who were switched from zoledronic acid to denosumab. During the blinded treatment phase, the incidences of ONJ in exposure-adjusted subjects were 49 (1.9%) and 31 (1.2%) in the denosumab and zoledronic acid groups, respectively. In total, 32 (6.9%) and 25 (5.5%) new cases of ONJ (not adjusted for exposure) were reported for patients continuing and switching to denosumab, respectively. The incidences of hypocalcemia were 4.3% and 3.1% in patients continuing and switching to denosumab, respectively, which are similar to the blinded treatment.

A major advantage of denosumab is its subcutaneous method of injection that can be administered quickly compared to zoledronic acid, which has to be given as an IV infusion for 30 minutes and can be challenging to give in an already busy clinical setting. Denosumab achieves its maximal concentration in blood 5–21 days after the injection contrary to zoledronic acid that shows a rapid decrease in the serum concentration. Another advantage of denosumab is that it does not require renal dose reduction. On the other hand, one of the most feared side effects that include ONJ is similar for both drugs, although hypocalcemia incidence is more frequent, especially during the early months of first administration. However, denosumab-related hypocalcemia may be obviated with adequate calcium and vitamin D supplementations.<sup>39</sup>

In addition, symptomatic skeletal-related events (SSEs) are a new end point introduced in recent studies. A reassessment of the phase III trial showed that denosumab reduced the risk of SSEs as compared to zoledronic acid.<sup>40</sup> Treatment with denosumab significantly reduced the risk of developing the first SSE [HR, 0.78; 95% CI, 0.66–0.93;  $P = 0.005$ ] and first and subsequent SSEs (rate ratio, 0.78; 95% CI, 0.65–0.92;  $P = 0.004$ ) compared to zoledronic acid.

Another large phase III trial evaluating the bone-metastasis-free survival in men who are at high risk of developing bone metastasis, such as those with elevated prostate-specific antigen (PSA) levels of  $\geq 8.0$  ng/mL or those with short PSA doubling time (PSADT) of  $\leq 10.0$  months or both, as determined by time to first occurrence of bone metastasis or death from any cause, accrued 1432 men who were randomly assigned to receive either 120-mg denosumab subcutaneously or placebo every four weeks.<sup>41</sup> Although no difference in OS or progression-free survival was seen between groups, denosumab was

shown to significantly increase bone-metastases-free survival by a median of 4.2 months (29.5 versus 25.2 months, HR: 0.85; 95% CI, 0.73–0.98;  $P = 0.028$ ). In a subset analysis, the patients with a shorter PSADT benefited the most from denosumab compared with placebo. Despite the positive findings of this trial, the end points were not deemed clinically significant or meaningful enough and the risk of potentially prolonged administration of denosumab was such that denosumab failed to gain the approval of the US FDA for this particular indication of delaying bone metastases.

### Radiopharmaceuticals

The other major class of bone-targeted agents in prostate cancer is the bone-seeking radiopharmaceuticals.<sup>42</sup> Radiopharmaceuticals have long been considered useful mainly as a palliative modality for patients with metastatic prostate cancer, and they have been underutilized mainly because of their notable side effect that is frequent and profound myelosuppression.<sup>43</sup> Radiopharmaceuticals emit either alpha or beta particles, both of which deliver damaging radiation to cancer cells. Alpha emitters have the advantage of shorter penetration range with higher transfer of linear energy, hence resulting in better cell-kill and DNA damage. Historically, the most commonly used radiopharmaceuticals are the beta emitters, strontium-89 (Sr-89) chloride (Metastron®; GE Healthcare), and samarium-153 (Quadramet®; EUSA Pharma). However, neither of these two agents showed OS benefit. The emergence of radium-223 and its OS benefit has revolutionized the use of radiopharmaceuticals in mCRPC.

**Strontium-89.** Sr-89 was initially approved by the US FDA in 1993 as the first radiopharmaceutical for mCRPC. It is a pure beta emitter that has a long half-life of 50.5 days, a beta energy of 1.5 MeV, and is rapidly renally excreted.<sup>44,45</sup> Sr-89 is a divalent ion, similar to calcium, which is preferentially taken up into the inorganic matter of bone, with a 10-fold affinity for metastatic bone compared to healthy bone.<sup>46,47</sup> An early phase trial initially reported a rather quick time to response of about nine days, with an average duration of response of 1.6 months in patients receiving doses ranging from 1.0 to 4.0 mCi/kg.<sup>48</sup> Similarly, a retrospective study of dose escalation studies found a positive correlation between increasing doses of Sr-89 with pain response.<sup>49</sup> The mean duration of pain relief reported in this study was about six months. Another study reported no dose-response relationship with increasing Sr-89 doses from 1.5 to 3.0 MBq/kg.<sup>44</sup> A systematic review of several randomized trials summarizing the efficacy of Sr-89 revealed the ability of strontium to result in complete pain response with an average of 32%.<sup>45</sup> While Sr-89 achieved pain response lasting with a mean duration of ~15 months, with decreased requirements for narcotics, the main limiting factor was its hematologic toxicity, making the treatment challenging for most patients.

**Samarium-153.** Samarium-153 conjugated to ethylenediaminetetra(methylenephosphonic) acid is another beta-emitting



radiopharmaceutical that was approved by the US FDA in 1997 at a dose of 1 mCi/Kg. Its half-life is 1.9 days, which is much shorter than Sr-89, and it provides rapid pain relief within two to seven days.<sup>50,51</sup> Contrary to Sr-89, samarium-153 is also a gamma emitter of 103 keV that allows for scintigraphic imaging correlating with conventional technetium-99 bone scans. Similar to Sr-89, myelosuppression remains the main adverse effect along with platelet and white cell counts that nadir by three to six weeks and generally recover by eight weeks.<sup>52,53</sup> After a single administration of 1.0 mCi/kg of samarium-153, mean platelet and white cell reductions were observed in close to half of patients.<sup>54</sup>

Contraindications to the use of beta-emitting radiopharmaceuticals include baseline myelosuppression, prior receipt of radiation in the preceding two months, impending spinal cord compression, significant renal dysfunction, Karnofsky performance status <50%, and disseminated intravascular coagulation.

**Radium-223.** Radium-223 dichloride (radium-223; Xofigo®, previously known as Alpharadin) is a novel radioisotope that emits cytotoxic alpha particles that have a high affinity for the bone matrix. Radium-223 acts as a calcium mimetic by forming complexes with the bone mineral hydroxyapatite in areas of high bone turnover, thereby directly targeting the areas of bone metastases.<sup>55</sup> Radium-223 is soluble in water as radium-223 chloride and, when administered intravenously, decays over six steps to lead-207, releasing for each atom four-alpha particles and two-beta particles, with alpha particles emitting 95.3% of the energy and beta particles emitting 3.6%. Only 1.1% of the energy emitted is gamma rays.<sup>56–58</sup> The released alpha particles are directly cytotoxic to cells by inducing double-stranded DNA breaks.

Contrary to the beta emitters, the renal excretion of radium-223 is minimal and it is excreted mainly through the gut with an 11.4-day half-life. Another major advantage of radium-223 is that the emitted radiation is more limited, with a much shorter track length of <0.1 mm in tissue (compared with 0.6 mm for samarium-153 and 2.4 mm for Sr-89), offering the advantage of less myelosuppression.<sup>59</sup> The pharmacokinetics, pharmacodynamics, and distribution of radium-223 were evaluated in a phase I trial that included 10 patients with metastatic prostate cancer to bone.<sup>60</sup> Radium-223 was rapidly cleared from the circulation, with only 0.5% of radium-223 remaining after 24 hours. The main excretion of the drug was gastrointestinal, with minimal renal excretion.

Early preclinical studies of radium-223 in rats demonstrated a bone distribution similar to that of Sr-89, with a bone marrow-sparing advantage and a selective concentration in bone rather than soft tissues, hence resulting in the exclusion of patients whose disease involves bulky adenopathy >3 cm. In addition, experimental rats that received chemotherapy and had bisphosphonate-resistant bone metastases showed longer survival when treated with radium-223.<sup>61</sup> In the same phase I trial,<sup>55</sup> the results showed a significant decline in serum alkaline phosphatase by half,

a significant pain response in 60% of patients, with mild and reversible myelosuppression. Given positive encouraging results, a phase II trial was initiated.<sup>62</sup> The phase II trial was a double-blind, randomized trial that evaluated the effect of radium-223 in patients with mCRPC who had either multiple bone metastases or one painful bone lesion with two consecutive rising PSA levels. The patients received external beam radiation and IV radium-223 at 50 kBq/kg for a total of up to four injections or external beam radiation and placebo. The two treatment arms showed a similar hematologic toxicity profile. The radium-223 arm showed better efficacy, with a greater reduction in alkaline phosphatase, a longer time to PSA progression, and an increased time to SREs. In addition, a trend for improved survival was noted when compared with the placebo arm (65.3 versus 46.4 weeks;  $P = 0.066$ ). These results were confirmed in the 24-month follow-up study, during which no increased rate of secondary malignancies was found.<sup>63</sup> Another double-blind, phase II study analyzed the effect of four different doses of radium-223 (5, 25, 50, and 100 kBq/kg) in 100 patients with mCRPC.<sup>64</sup> Pain reduction was noted as early as two weeks after the injection, and after eight weeks, 40%, 63%, 56%, and 71% of patients in the 5, 25, 50, and 100 kBq/kg groups, respectively, had pain reduction, and no major adverse events were noted. The positive results of the phase II trials led to the initiation of the landmark Alpharadin in Symptomatic Prostate Cancer (ALSYMPCA) trial.

The ALSYMPCA trial is the landmark trial that demonstrated significant improvement in OS utilizing a bone-seeking radiopharmaceutical.<sup>65</sup> This phase III, randomized, placebo-controlled trial enrolled 922 symptomatic patients with an mCRPC across 19 countries, having at least two metastatic sites on scintigraphy in the absence of visceral metastases, although adenopathy of <3 cm was allowed. Patients were pretreated with docetaxel, intolerant of docetaxel, or refused to take prior docetaxel. Randomization was performed in a 2:1 double-blind fashion with one arm of patients receiving six cycles of IV radium-223 on a four-week schedule with the best standard of care versus six infusions of placebo with the best standard of care. The patients were enrolled from June 2008 to February 2011. The arms of the study were balanced in terms of baseline characteristics. The median age of the patients was 71 years. In both arms, 57% of the patients have previously received docetaxel. In the middle of 2011, a planned interim analysis showed a survival benefit of radium-223 and the trial was stopped early. Updated analysis continues to demonstrate improvement in the survival at 14.9 months for radium versus 11.3 months for those receiving placebo ( $P = 0.00185$ ; HR = 0.695). Secondary end points all favored radium-223. Notably, the number of SREs was reduced and the median time to an SRE was prolonged in the radium-223 arm by around six months (15.6 versus 9.8 months; HR: 0.66; 95% CI, 0.52–0.83;  $P = 0.00037$ ).<sup>66</sup> Other secondary end points (PSA response, time to PSA progression, and change in alkaline



phosphatase) were also in favor of radium-223. In addition, a higher percentage of patients in the radium-223 arm had a significant improvement in their quality of life, as assessed by the Functional Assessment of Cancer Therapy-Prostate score (25% versus 16%;  $P=0.02$ ). Radium-223 seemed more tolerable than older generations of radiopharmaceuticals. Most notably, the incidence of grade 3 and 4 anemia, neutropenia, and thrombocytopenia was minimal (1.8%, 0.7%, and 3.2%, respectively). Interestingly, more adverse events occurred in patients treated with placebo than in those treated with radium-223 (96% versus 93% all grade adverse events, respectively). In the subgroup analysis looking at patients with prior docetaxel exposure, a higher incidence of grade 3 and 4 thrombocytopenia was shown in those who received radium-223 at 9% (31 of the 347 patients) versus only 3% (5 of the 171 patients) in the placebo group, but no differences in grade 3 and 4 anemia or neutropenia were seen in either treatment group.<sup>67</sup>

This trial formed the basis of approval by the US FDA of radium-223 on May 15, 2013, for mCRPC patients who have painful bone metastases and no visceral metastases. The US FDA-recommended dose and schedule constitutes 50 kBq/kg (1.35 microcuries/kg) administered intravenously over one minute every four weeks for six doses. To be eligible for treatment, patients were required to have adequate bone marrow function.

The enrolled patients in the ALSYMPCA trial entered a designated three-year follow-up program after receiving six injections of radium-223 or placebo.<sup>68</sup> A total of 574 patients from 921 patients entered the follow-up program ( $n = 406$  received radium-223 and  $n = 168$  received placebo). A total of 322 patients in the radium-223 group withdrew from the follow-up program (79%) and 144 withdrew from the placebo arm (86%), the most common cause being death. The median duration of follow-up was 10.4 months for the radium-223 group and 7.6 months for the placebo group. Only 20 patients (16 in the radium-223 group and 4 in the placebo group) completed the three-year follow-up. In addition, long-term follow-up of the ALSYMPCA trial at 1.5 years showed that radium-223 continues to be very safe, with no increased incidence of second cancers or hematological malignancies.

Data from 696 Expanded Access Program (EAP) patients recruited from 14 countries were recently presented.<sup>69,70</sup> In this prospective phase IIIb study, mCRPC patients with symptomatic or asymptomatic bone metastases and no visceral disease received up to six cycles of radium-223. Of the studied patients, 60% received prior therapy with docetaxel and 22% were cotreated with abiraterone, 20% with denosumab, 18% with bisphosphonates, and 4% with enzalutamide. A total of 58% received all six radium-223 injections. Patients who received both abiraterone and enzalutamide before radium-223 treatment seemed less likely to receive all the assigned six cycles of radium-223 than those who had not received either of these hormonal therapies (31% versus 57%;  $P=0.003$ ). Whether this suggests a benefit perhaps to earlier use of radium in these patients or simply reflects the overall

worse prognoses of men who have received either hormonal therapies and failed through them and hence unable to complete all six cycles is unknown.

Grade 3 and 4 adverse events were reported in 38% of patients, and only 21% discontinued radium-223 due to side effects. At the time of analysis, median OS was 16 months and median time to first SSE was 18 months; 8% had >50% confirmed PSA decrease from baseline. In a post hoc analysis, OS was statistically significantly longer in patients with a good ECOG PS, no baseline pain, low alkaline phosphatase, and concomitant denosumab or abiraterone use. The toxicity profile of radium-223 was consistent even in patients receiving other therapies. The EAP showed that the survival benefit was similar and even more prolonged compared to the ALSYMPCA trial probably due to the earlier use of radium-223 in the EAP.

Given these updated analyses, albeit many in the post hoc analyses setting, the timing of the use of radium-223 in the treatment sequence of mCRPC remains a challenging and unanswered question, especially given the vast availability of a wide range of therapies ranging from chemotherapy, oral androgen inhibitors, and other bone-targeted therapies. The mechanism of action of radium-223 would not appear to prohibit or limit usage of other available systemic therapies in mCRPC, and while the pivotal ALSYMPCA trial only allowed use of the best supportive therapy with older agents, such as ketoconazole, newer androgen-targeting agents such as abiraterone or enzalutamide can conceivably be combined with radium and is the topic of several ongoing investigational trials to date (see Table 2). The efficacy of radium-223 seems to be independent of prior use of docetaxel, and its safety profile seemed similar both in the predocetaxel and postdocetaxel setting, except for the expected higher hematologic toxicity and nausea and vomiting in the postdocetaxel setting and unexpectedly higher benefit in delaying SREs in the postdocetaxel setting than those in the predocetaxel setting. There may be a subset of few patients who can benefit beyond the six cycles that are given in the pivotal trials, but giving radium-223 beyond the approved six cycles remains investigational.

### Combination of Bone-Targeted Agents

With the availability of multiple different agents that target bone in mCRPC, the potential combination of those agents is an interesting question. The possibility of combining radium and docetaxel was examined in a phase 1/2a trial, and the combination was found to be safe and efficacious.<sup>71</sup> However, the dose of docetaxel selected for the phase 2a portion had to be reduced from 75 mg/m<sup>2</sup> to 60 mg/m<sup>2</sup> every three weeks (for 10 cycles) with the standard radium of 50 kBq/kg IV but given every six weeks instead of every four weeks (for 5 cycles). This combination is compared to docetaxel 75 mg/m<sup>2</sup> every three weeks. Preliminary data from the trial were recently presented, and the combination was found to be well tolerated with a greater percentage of patients completing the planned therapy

**Table 2.** Select ongoing clinical trials involving bone-targeted therapies in mCRPC.

CLINICAL TRIAL NAME	PHASE	POPULATION/ESTIMATED ENROLLMENT (N)	PRIMARY ENDPOINTS	TREATMENT ARMS	CLINICAL TRIAL IDENTIFIER
PEACEIII	Phase III	Chemotherapy-naïve minimally symptomatic mCRPC/n = 560	Radiographic progression free survival	Enzalutamide vs Enzalutamide + Radium 223 (Ra-223)	NCT02194842
ERA 223	Phase III	Chemotherapy-naïve minimally symptomatic mCRPC/n = 800	Symptomatic skeletal event free survival	Abiraterone vs Abiraterone + Radium 223	NCT02043678
Non-Randomized trial assessing pain efficacy with radium-223 in symptomatic mCRPC	Phase II	Symptomatic mCRPC/n = 15	Pain response	Radium-223	NCT02278055
Re-treatment safety of radium-223 dichloride in CRPC with bone metastases	Phase I/II	Symptomatic mCRPC who received prior 6 cycles of Ra-223/n = 44	Treatment related adverse events	Radium-223	NCT01934790
Radium 223 in CRPC bone metastases	Observation, open label	mCRPC/n = 25	Markers predicting overall survival	Radium-223	NCT02135484
Radium-223 dichloride (Ra-223 Cl <sub>2</sub> ) asian population study in the treatment of CRPC patients with bone metastasis	Single-arm	mCRPC/n = 234	Overall survival, adverse events	Radium-223	NCT01810770
A randomized phase IIa efficacy and safety study of radium-223 dichloride with abiraterone acetate or enzalutamide in mCRPC	Phase II	mCRPC/n = 66	Bone scan response	Radium-223 vs Radium-223 + abiraterone vs Radium-223 + enzalutamide	NCT02034552
Open label phase 2 trial of Ra- 223 with concurrent administration of AA plus prednisone in symptomatic CRPC subjects with bone metastasis (eRADicAte)	Phase II	mCRPC/n = 40	Bone pain	Radium-223 + abiraterone	NCT02097303
Radium Ra 223 with enzalutamide in men with mCRPC	Phase II	mCRPC/n = 50	Bone formation markers	Radium-223+ enzalutamide vs Enzalutamide	NCT02199197
Prevention of symptomatic skeletal events with denosumab administered every 4 weeks versus every 12 weeks	Phase III	Metastatic breast or prostate cancer receiving chemotherapy/n = 1380	Time to first symptomatic skeletal event	Denosumab every 4 weeks vs Denosumab every 12 weeks	NCT02051218

(64% versus 38%). Another interesting question is the efficacy of the coadministration of radium and bisphosphonates. In the ALSYMPCA trial, 41% of the patients were on bisphosphonate prior to enrollment. Although patients not using bisphosphonates at study entry had a trend toward delay in SSEs with radium-223 (11.8 versus 8.4 months; HR: 0.77;  $P = 0.07$ ), there was a significant delay in SSEs in patients using bisphosphonates (19.6 versus 10.2 months; HR: 0.49;  $P = 0.00048$ ). This observation perhaps suggests some synergism between radium-223 and bisphosphonates, although further studies are needed to validate this finding. Data from the EAP also suggest a possible positive interaction with denosumab.

Therefore, continuation of bone-targeted therapies even while patients are started on radium-223 would seem beneficial.

Another interesting combination with nonoverlapping toxicity profile is the combination of radium with the novel hormonal agents abiraterone and enzalutamide. A phase III trial is evaluating the combination of radium with enzalutamide in patients with asymptomatic or minimally symptomatic mCRPC in a phase 3 trial conducted by the Prostate Cancer Consortium in Europe (PEACE; NCT02194842; Table 2). Another phase 3 trial (ERA 223; NCT02043678) is evaluating radium-223 with abiraterone in subjects with minimally symptomatic, chemotherapy-naïve mCRPC (NCT02043678).



## Conclusions and Future Directions

Increasing efforts directed at targeting the bone microenvironment have led to the approval of the US FDA of these aforementioned agents (see Table 1). Several attempts at improving the bone-targeted therapy approach brought about the study of varying agents that were felt to have initial promising effects in this arena, such as dasatinib and cabozantinib. Dasatinib is a tyrosine kinase inhibitor against Src that has a role in the promotion of bone metastases by directly interacting with osteoclasts and prostate cancer cells. However, enthusiasm for the drug was dampened after it was studied in a phase III, randomized, placebo-controlled trial along with docetaxel but failed to meet the primary end point of OS.<sup>72</sup> Cabozantinib is an oral multiple tyrosine kinase inhibitor of vascular endothelial growth factor and MET and RET. The phase II trial of cabozantinib showed unprecedented responses in the bone (12% complete response)<sup>73</sup> which led to two phase III trials, namely, COMET-1 and COMET-2, looking at survival and pain end points although disappointingly negative.<sup>74</sup> Other prevailing questions and observations in this area include the observed beneficial effects of other approved novel androgen-targeted signaling agents (abiraterone and enzalutamide) on SREs, raising the question of whether it is even necessary to add or continue with bone-targeted therapies (see Table 2 for a list of bone-targeted therapies in clinical trials either as monotherapy or in combination with other agents). A post hoc analysis of the COU-AA-302 trial showed that addition of bone-targeted agents, compared to the patients who did not receive any bone-targeted agents, had better OS (HR: 0.75;  $P = 0.01$ ) as well as longer time before deterioration in performance status,<sup>75</sup> highlighting the need for continued use of bone-targeted agents, even while on therapies that are already being used for antitumor effects. Ultimately, identifying resistance mechanisms to therapies that target the bone or bone microenvironment would help in advancing the field further. For instance, recent discovery of paracrine mechanisms of resistance niches in the tumor-induced bone may help identify additional therapeutic targets such as the integrin signaling pathways and leverage combinational agents to avert resistance to conventional therapies.<sup>76</sup>

The advances over the past decade of targeting the bone microenvironment have brought about promising effects in improving the quality of life of men afflicted with bone metastatic disease, and efforts to continually devise more molecularly targeted therapy will hopefully help to combat this disease and also improve survival.

## Author Contributions

Conceived the concepts: JEA, JAC. Analyzed the data: JEA, JAC. Wrote the first draft of the manuscript: JEA, JAC. Contributed to the writing of the manuscript: JEA, JAC. Agree with manuscript results and conclusions: JEA, JAC. Jointly developed the structure and arguments for the paper:

JEA, JAC. Made critical revisions and approved final version: JEA, JAC. Both authors reviewed and approved of the final manuscript.

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