Radium-223 chloride: a potential new treatment for castration-resistant prostate cancer patients with metastatic bone disease

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Background: Radium-223 chloride (^{223}Ra ; Alpharadin) is an alpha-emitting radioisotope that targets areas of osteoblastic metastasis and is excreted by the small intestine. When compared with beta-emitters (eg, strontium-89, samarium-153), ^{223}Ra delivers a high quantity of energy per track length with short tissue penetration.

Objective: This review describes the mechanism, radiobiology, and preclinical development of ^{223}Ra and discusses the clinical data currently available regarding its safety and efficacy profile.

Methods: Data from clinical trials including abstracts were collected and reviewed using the PubMed Database, as well as the American Society of Clinical Oncology abstract database.

Conclusion: Current bone-targeted therapies fall into two main categories: antiresorptive agents (eg, zoledronic acid, denosumab), which have been shown to delay skeletal-related events, and radiopharmaceuticals (eg, samarium-153), which may have a role in pain palliation. Historically, neither antiresorptive agents nor radiopharmaceuticals have shown definitive evidence of improved overall survival or other antitumor effects in metastatic castrate-resistant prostate cancer (mCRPC). Radiopharmaceuticals are limited by myelosuppression, thrombocytopenia, and renal excretion. In a recently reported randomized Phase III trial in men with symptomatic bone-metastatic CRPC who had received or were ineligible for docetaxel chemotherapy, ^{223}Ra treatment resulted in improved overall survival and delayed skeletal-related events. Toxicity consisted of minor gastrointestinal side effects and mild neutropenia and thrombocytopenia that were rarely severe. Pending regulatory approval, ^{223}Ra may represent a unique and distinct option for an important subgroup of patients with mCRPC; future trials should address its use in combination or in sequence with existing and novel agents.

Keywords: Alpharadin, ^{223}Ra , radium-223, radionuclide therapy, metastatic castrate-resistant prostate cancer, bone metastases

Introduction

Prostate cancer is the most common cancer in men and the second-leading cause of cancer death in men, with 241,740 new diagnoses and 28,170 deaths projected in the US in 2012.¹ Advanced prostate cancer has a penchant to metastasize to bone, possibly due to osteomimicry or altered adhesion molecules.^{2,3} Among patients with metastatic, castrate-resistant prostate cancer (mCRPC) treated with first-line chemotherapy, almost 90% have radiographic evidence of bone metastasis.^{4,5} Morbidity from complications of osseous metastases, such as pathologic fractures, spinal cord compression, and pain, greatly impairs the quality of life of patients with mCRPC. In addition, pain due to mCRPC is a strong independent prognostic factor for death, and is included in contemporary nomograms for survival in this disease,⁶⁻⁹ thus agents that can reduce pain

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and suffering due to metastatic prostate cancer may improve not only quality of life but also quantity of life.

Mitoxantrone chemotherapy and several radioisotopes, such as samarium-153 (^{153}Sm) and strontium-89 (^{89}Sr), were the first therapies approved for palliation of bone pain in patients with mCRPC, but without evidence of improvement in overall survival.^{10,11} Since 2004, four systemic therapies have been approved on the basis of improvements in overall survival, with varying effects on bone pain and skeletal complications.^{4,5,12–14} These agents, particularly the taxanes docetaxel (Taxotere®; Sanofi-Aventis, Bridgewater NJ), cabazitaxel (Jevtana®; Sanofi-Aventis), and the novel androgen biosynthesis inhibitor abiraterone acetate (Zytiga®; Janssen Biotech, Inc, Horsham, PA), have direct antitumor effects that may result in pain palliation. Contemporaneously, two osteoclast inhibitors (zoledronic acid [Zometa®; Novartis AG, Basel, Switzerland] and denosumab [Xgeva®; Amgen Inc, Thousand Oaks, CA]) have been approved on the basis of delay of skeletal-related events (SREs; pathologic fracture, spine cord compression, and requirement for radiation or surgery to bone), but without improvements in overall survival (OS).^{15,16} In addition, the novel androgen signaling inhibitor MDV3100 (enzalutamide, Xtandi®; Medivation, Inc, San Francisco, CA) has demonstrated improvements in OS and palliative end points; its approval was granted August 31, 2012, as this article went to press.^{17–19} Prior to the development of ^{223}Ra (Alpharadin®; Algeta ASA, Oslo, Norway/Bayer AG, Leverkusen, Germany), no specifically bone-targeted therapy has been shown to improve median OS in the population of patients with mCRPC with osseous metastases.

Survival-prolonging systemic therapies currently approved for mCRPC include docetaxel, cabazitaxel, sipuleucel-T

(Provenge®; Dendreon, Seattle, WA), abiraterone, and MDV3100 (Table 1). However, the effects of these therapies on skeletal complications are not well reported. Pain response is the only SRE that has been routinely reported (Table 2), with much fewer data on prevention or delay of SREs. A special case to this has been sipuleucel-T, which is specifically indicated for men with mCRPC who have minimal to no symptoms. As a reference, the palliative chemotherapy regimen of mitoxantrone/prednisone demonstrated a 29% response on the Present Pain Intensity (PPI) scale versus 12% with prednisone alone ($P=0.01$), with a duration of 43 versus 18 weeks ($P<0.0001$).¹⁰ The landmark TAX-327 study showed a pain response of 35% versus 22% ($P=0.01$) on the PPI scale for docetaxel/prednisone versus mitoxantrone/prednisone, with a duration of 3.5 versus 4.8 months (P not significant).⁵ Patients who experienced a pain response in this trial were found to have improved overall survival as compared with those men without such a response.⁷ In the post-docetaxel mCRPC setting, cabazitaxel/prednisone showed no improvement over mitoxantrone/prednisone on the PPI scale (9.2% vs 7.7%; $P=0.63$; duration not reached) in the TROPIC trial.¹³ In a similar post-docetaxel setting, the COU-AA-301 study demonstrated a 44% versus 27% pain response on the Brief Pain Inventory (BPI) scale for abiraterone/prednisone vs placebo/prednisone, with a time to progression of approximately 8 versus 5 months (25th percentile; $P=0.0056$).²⁰ The great variability in pain response for the control arms (7.7% for mitoxantrone/prednisone in the TROPIC study, and 27% for prednisone alone in the COU-AA-301 study) suggests great variability in the reporting methods. Notably, in the COU-AA-301 study, the time to SRE was also delayed to approximately 10 versus 5 months ($P=0.0006$). There were previously no other data

Table 1 Overall survival benefit in recent Phase III trials in mCRPC

Agent (trial, year)	Disease state	Comparator	Hazard ratio	Median OS, months (P-value)	FDA approval
Sipuleucel-T (IMPACT, 2010) ¹²	Chemonaive mCRPC; asymptomatic or minimally symptomatic	Placebo	0.775	25.8 vs 21.7 (0.032)	Yes
Docetaxel + prednisone (TAX-327, 2004) ⁵	Chemonaive mCRPC	Mitoxantrone + prednisone	0.76	18.9 vs 16.5 (0.009)	Yes
Cabazitaxel + prednisone (TROPIC, 2010) ¹³	Post-docetaxel mCRPC	Mitoxantrone + prednisone	0.70	15.1 vs 12.7 (<0.0001)	Yes
Abiraterone + prednisone (COU-AA-301, 2010) ¹⁴	Post-docetaxel mCRPC	Placebo + prednisone	0.65	14.8 vs 10.9 (<0.001)	Yes
MDV3100 (AFFIRM, 2012) ¹⁷	Post-docetaxel mCRPC	Placebo	0.631	18.4 vs 13.6 (0.0001)	Yes
Radium-223 (ALSYMPCA, 2012) ³⁵	Bone-metastatic mCRPC; symptomatic	Placebo + BSC	0.695	14.0 vs 11.2 (0.00185)	Pending

Abbreviations: mCRPC, metastatic castrate-resistant prostate cancer; OS, overall survival; BSC, best standard of care.

Table 2 Pain responses in randomized studies of survival prolonging therapies in mCRPC

Agent	n (% with pain)	Pain scale*	Pain response (P-value)	Duration (months)
Docetaxel + prednisone ⁵	1006 (45%)	PPI	35% vs 22% (0.01)	3.5 vs 4.8 (NS)
Cabazitaxel + prednisone ¹³	755 (45%)	PPI	9.2% vs 7.7% (0.63)	NR
Abiraterone + prednisone ^{14,20}	1195 (44%)	BPI	44% vs 27% (0.0002)	8 vs 5 (<i>P</i> = 0.0056) [†]

Notes: [†]25th percentile. *Of note, many of these trials used differing pain scales and variable incorporation of composite analgesic scores; thus, cross-trial comparisons are not possible.

Abbreviations: mCRPC, metastatic castrate-resistant prostate cancer; PPI, Present Pain Intensity; NS, not significant; NR, not reached; BPI, Brief Pain Inventory.

regarding prevention or delay of SREs with the other survival-prolonging systemic therapies.

Bone-targeted osteoclast inhibitors and bone-seeking radiopharmaceuticals have been approved for mCRPC on the basis of prevention or delay of SREs and palliation of pain, respectively. Zoledronic acid, a bisphosphonate that inhibits osteoclasts, significantly delayed the time to SRE versus placebo (approximately 16 versus 11 months, *P* = 0.009) and also improved pain and analgesia scores.^{15,21} More recently, a monoclonal antibody to the receptor activator of NF-κB ligand (RANKL), denosumab, has also been approved. In a placebo-controlled Phase III trial, denosumab showed a 3.6-month improvement in time to first SRE over zoledronic acid (20.7 versus 17.1 months; *P* = 0.0002 [noninferiority], *P* = 0.008 [superiority]).¹⁶ Of note, neither zoledronic acid nor denosumab demonstrated improvements in prostate-specific antigen (PSA) levels, overall disease progression, or overall survival. Thus, while these are bone-targeted agents, they may have a greater effect on bone health and quality than on the tumor microenvironment, which supports metastatic cancer and promotes treatment resistance. An ideal tumor microenvironment-targeting agent would thus not only prevent symptomatic deterioration but also improve upon disease-related outcomes, particularly OS.

In addition to osteoclast inhibitors, therapeutic radioisotopes that have a predilection to accumulate in bone turnover sites can be administered. These radiopharmaceuticals emit

either alpha or beta particles. An alpha particle, which is ejected from a heavy nucleus during alpha decay, consists of two neutrons and two protons (ie, a helium nucleus).²² A beta particle is an electron released from a nucleus containing excess neutrons during beta decay, in which one neutron is converted to a proton, an electron, and a neutrino.²² Both α- and β-particles can deliver damaging radiation locally to cancerous cells. The most commonly used radiopharmaceuticals, both β-emitters, currently approved in the US for treatment of bone metastases are ⁸⁹Sr (Metastron®; GE Healthcare, Arlington Heights, IL) and ¹⁵³Sm (Quadramet®; EUSA Pharma, Oxford, UK). There are key differences in the physical properties of these radioisotopes, which have important clinical implications (Table 3). ⁸⁹Sr is a pure β-emitter with a long half-life (50 days), whereas ¹⁵³Sm has a much shorter half-life (1.9 days) and is also a γ-emitter, which allows posttreatment scintigraphic imaging. In addition, ⁸⁹Sr emits higher-energy beta particles, resulting in greater tissue penetration and consequently higher bone marrow toxicity. Multiple randomized trials have been conducted with ⁸⁹Sr and ¹⁵³Sm in patients with mCRPC.^{23–29} There was no demonstration of improvement in overall survival in Phase III trials, although palliative benefits were seen that formed the basis of US FDA approval. One recent meta-analysis concluded that, although there is some evidence that these beta-emitting radioisotopes might provide a small benefit with complete reduction in pain over 1–6 months and no increase in analgesic use, severe adverse effects (mainly leukopenia and thrombocytopenia) are relatively frequent.¹¹ Nonetheless, ¹⁵³Sm can be administered in repeat doses, once hematologic toxicities have recovered, for persistent pain.³⁰ Other limitations to ⁸⁹Sr and ¹⁵³Sm include the fact that they are renally excreted; this is not ideal in patients with genitourinary cancers. Overall, ⁸⁹Sr and ¹⁵³Sm might provide some palliative of pain, at the potential expense of significant hematologic toxicities and without demonstrated OS benefit. Ongoing work of these agents in combination with chemotherapy may optimize their efficacy.^{31–34}

In comparison to beta-emitting radioisotopes, radium-223 (²²³Ra; Alpharadin®, Algeta) is an α-emitter that delivers

Table 3 Properties of selected radiopharmaceuticals for treatment of bone metastases in mCRPC

Radionuclide	Particle	Primary excretion	Physical half-life (days)	Particle energy in MeV	Tissue range (mm)	Bone surface to red bone marrow dose ratio
Radium-223 (Alpharadin®) ³⁸	Alpha	Small bowel	11.4	5.56	<0.1	10.3
Samarium-153 (Quadramet®) ^{76*}	Beta	Kidney	1.9	0.81	3	4.4 [†]
Strontium-89 (Metastron®) ^{77*}	Beta	Kidney	50.5	1.46	8	1.6 [†]

Notes: [†]Values in these rows taken from prescribing information^{75,76} insert unless otherwise noted. [†]Calculated based on values in product's prescribing information.

Abbreviations: mCRPC, metastatic castrate-resistant prostate cancer; MeV, mega-electronvolts.

radiation with a higher biologic effect to a more localized area. In a large randomized Phase III trial, ^{223}Ra has recently demonstrated improvements in OS, time to first SRE, and biochemical parameters, with a remarkably tolerable adverse-event profile, in men with bone-metastatic CRPC.³⁵ While ^{223}Ra has not yet been approved for use in the US, and there is little experience in the US with the use of this agent, it represents the first bone-targeted therapeutic radiopharmaceutical to demonstrate a survival benefit, which has been the benchmark for recent FDA approvals in this disease setting. An expanded access trial of ^{223}Ra in men with mCRPC with bone metastases is planned.³⁶ Many questions have arisen as to the appropriate sequencing of existing and novel therapies with ^{223}Ra and if/how to combine ^{223}Ra with these systemic therapies. This manuscript will review the preclinical and clinical development of ^{223}Ra , and comment on its potential role and use in the armamentarium of therapy for mCRPC.

Radiobiology, mechanism of action, and preclinical development of ^{223}Ra

Bone-seeking therapeutic radiopharmaceuticals are unique among anticancer therapies in that they actually target the stroma rather than the tumor itself: the target is calcium hydroxyapatite in bone. Ionizing radiation can thus be selectively delivered to areas of increased osteoblastic activity, allowing the targeting of multiple metastases simultaneously, including both symptomatic as well as asymptomatic lesions. As mentioned above, the commonly used clinically available radiopharmaceuticals are β -emitters, with ^{89}Sr and ^{153}Sm the most well studied.³⁷ Following injection of ^{89}Sr , radiation doses are delivered to the osseous target lesions at low dose rates.³⁸ Between 16 weeks and 1 year, absorbed doses in the 20–40 Gy range are deposited as a steadily declining dose rate.^{39,40} Because of its higher dose rate and the shorter range (ie, tissue penetration), ^{153}Sm may have an improved therapeutic index compared with that of ^{89}Sr (Table 3).³⁸ Due to its relatively shorter half-life, repeated administration of ^{153}Sm is feasible for persistent or recurrent bone pain provided adequate hematologic function returns; however, effects on bone marrow remain a limitation.³⁰ This suggests that an agent with less depth of tissue penetration but similar or higher biologic effect is needed to facilitate repeated dosing. One potential reason for difficulty demonstrating antitumor and survival benefits with β -emitters could be related to this dosing limitation.

Cationic radium is a calcium mimetic (located in the same column of the periodic table as calcium), and as such naturally targets areas of bone turnover without the need

for a carrier. (Recall that the bone stores 99% of the human body's calcium and 85% of the phosphorous. Blood levels of calcium and bone resorption/formation are both tightly regulated by various hormones.⁴¹) For example, Radium-224 (^{224}Ra) has been used extensively for treatment of ankylosing spondylitis, a chronic inflammatory disease of the axial skeleton characterized by new bone formation.⁴² ^{223}Ra has a half-life of 11.4 days, produces four alpha particles from decay through short-lived daughter radionuclides, and has advantages over ^{224}Ra in terms of the decay chain.⁴³ ^{223}Ra was selected for biomedical applications based on its favorable decay chain and half-life.⁴³ In contrast to β -emitters, which have a low linear energy transfer (LET) and track lengths of up to several millimeters, α -emitters deliver a much more densely ionizing (high LET) radiation with an immense quantity of energy per track length and much shorter tissue penetration (<100 μm , or 2–10 cell diameters). The key physical differences in selected α - and β -emitters are summarized in Table 3, and the mechanism of action of ^{223}Ra is summarized in Figure 1. Because alpha-particle irradiation induces mostly double-stranded DNA breaks, cellular repair mechanisms may be less effective.⁴⁴ Lesions with clones of tumor cells remaining dormant in G_0 of the cell cycle may be eradicated by high LET radiation from α -emitters.^{38,45} In addition, the limited penetration depth also results in lower radiation dose to the marrow and other adjacent normal tissues.

Radiation safety precautions associated with ^{223}Ra therapy are minimal. Following therapy with ^{223}Ra , the risk of radiation exposure to others is very small, with the main recommendation being to maintain good hygiene. While ^{153}Sm and ^{89}Sr are excreted primarily by the kidneys, the major route of excretion of ^{223}Ra is through the feces, with only a small fraction of renal excretion; this reduces the chances of contamination. The patient's external radiation exposure to others is low enough to allow patients to be

Figure 1 Mechanism of action for the targeting of osseous metastases by ^{223}Ra . Reprinted with permission from Algeta ASA, from 2012 ASCO GU Symposium presentation.

Abbreviation: ^{223}Ra , radium-223.

immediately released under 10 CFR 35.75 following ²²³Ra administration.

Preclinical studies of ²²³Ra demonstrated its potential to be bone marrow-sparing, with promising antitumor activity and favorable biodistribution. In mice, bone uptake of ²²³Ra compared with ⁸⁹Sr was similar; however, estimates of dose to marrow cavities showed that ²²³Ra could be less toxic to bone marrow than β -emitters.⁴⁶ In a nude rat model of osseous metastases resistant to chemotherapy and biphosphonates, rats treated with ²²³Ra had superior symptom-free survival.⁴⁷ A biodistribution study in a dog with bone cancer injected with ²²³Ra showed elimination via intestinal clearance, with low activity in the intestinal wall that was similar to other soft tissues.³⁸ In addition, examination of these canine specimens using α -track microautoradiography demonstrated some concentration of the α -emitter on the surfaces of trabecular bone and a very high accumulation in the osteoblastic bone matrix.

Clinical evaluation of ²²³Ra Phase I studies

Based on the promising preclinical results, a Phase I dose-escalation and safety study was conducted in 25 men and women with prostate (n = 15) and breast (n = 10) cancers (AT1-BC-1).⁴³ Five patients were treated with a single dose of ²²³Ra at each of the following dose levels and followed for 8 weeks: 46, 93, 163, 213, or 250 kBq/kg. Subjects were followed for 8 weeks. The patients were observed for dose-limiting toxicity (defined as platelets < 20 × 10⁹/L or neutrophils < 0.5 × 10⁹/L) and adverse events (AEs). In addition, the blood-clearance profile of ²²³Ra was evaluated at 10 minutes and at 1, 4, 24, and 48 hours and 7 days postinjection. Gamma camera scintigraphy was performed in six patients, using the 271 keV peak of the ²¹⁹Rn daughter to indicate the position of its mother nuclide; this required long acquisition times due to the low number of events. Pain was assessed using the European Organization for Research and Treatment of Cancer QLQ-C 30 questionnaire at baseline, 1, 4, and 8 weeks.

Overall, ²²³Ra was well-tolerated, and no dose-limiting hematologic toxicity was observed.⁴³ Reversible myelosuppression was observed, with nadir counts occurring 2–4 weeks after administration of ²²³Ra. There was a trend towards increased myelosuppression at higher dose levels. Interestingly, there was more neutropenia than thrombocytopenia (in contrast to β -emitters, with which thrombocytopenia is often more frequent). There was no anemia above grade 2 or thrombocytopenia above grade 1

observed. Grade 3 leukopenia and neutropenia were only seen at the ≥ 163 kBq/kg doses in the same two patients, in addition to one isolated instance of leukopenia. The most common AEs were: transient diarrhea (40% of subjects); bone pain, including “flare” (36%); fatigue (25%); nausea (25%); and vomiting (25%). Whereas transient diarrhea was observed at all dose levels, nausea and vomiting occurred at the higher dose levels. AEs were generally mild, reversible, and manageable with supportive care (ie, antidiarrheal medication).

Blood radioactivity levels decreased from 12% of the initial at 10 minutes postinjection to 6% at 1 hour and <1% after 24 hours. By gamma scintigraphy, ²²³Ra appeared to accumulate in osteoblastic metastases, correlating well with conventional diagnostic ^{99m}Tc-MDP bone scans. Serum alkaline phosphatase decreased in both groups of patients, but was greatest in the patients with prostate cancer (-52.1 ± 14.8 , mean $\pm$ standard deviation) and significantly different between the groups ($P = 0.0028$). The 16 patients with an elevated serum alkaline phosphatase at baseline (of which eleven had prostate cancer) had a particularly robust decline, which was significantly different than patients with normal-range alkaline phosphatase at baseline. Pain palliation was noted in more than half of the patients, with 52% reporting improvement at 1 week, 60% at 4 weeks, and 56% at 8 weeks. Of note, a “flare” response (transient increase in bone pain) was observed in about one-fifth of patients (seven of 25) during the first week of treatment. This was the first clinical trial of an α -emitter for treatment of cancer patients with osseous metastases.

Because of a very tolerable toxicity profile (including mild myelosuppression and gastrointestinal side effects), pharmacodynamic effects consistent with the hypothesized mechanism of action (decline in serum alkaline phosphatase and correlation of gamma scintigraphy with bone scans), and evidence of clinical benefit (improved pain scores compared with baseline in up to 60%), ²²³Ra was deemed to be promising for further study. Also of note, survival in this Phase I study was observed to be greater than 20 months (with >20 months’ follow-up), which compared favorably to a contemporary Scandinavian randomized trial with ⁸⁹Sr in a similar population.⁴⁸ An additional Phase Ib study (BC1-05) of six patients with advanced prostate cancer demonstrated the feasibility of repeat dosing of ²²³Ra, but has only been reported in abstract form.^{38,49} Finally, a separate Phase Ib study (BC1-08) in men with progressive CRPC and two or more bone metastases on bone scan (n = 10) did not reach the maximum tolerated dose with escalation up to 200 kBq/kg and demonstrated targeting of osseous lesions,

rapid blood clearance, and excretion through the small intestine followed by transit through the large intestine.⁵⁰

Phase II studies

Two randomized, multicenter Phase II studies in patients with mCRPC have been published. In the first double-blind, placebo-controlled study (BC1-02), patients were randomized to be given either four intravenous injections of ²²³Ra at 50 kBq/kg or placebo every 4 weeks.⁵¹ In the second double-blind, dose-response study (BC1-04), patients were randomized to a single intravenous injection of ²²³Ra at 5, 25, 50, or 100 kBq/kg.⁵²

The first study (BC1-02) aimed to evaluate the effects of repeated ²²³Ra dosing in men with symptomatic CRPC.⁵¹ Patients were required to have multiple osseous metastatic lesions or one painful lesion with two consecutive rising PSA values. In addition, all patients had bone pain requiring external-beam radiotherapy (EBRT) and either had bilateral orchiectomy or else were maintained on a luteinizing hormone-releasing hormone agonist during the study. Patients were randomized to receive either four consecutive monthly injections of ²²³Ra at 50 kBq/kg or saline. EBRT was given to the most painful bony lesion starting no later than 7 days after the first injection. The primary end points were the mean change in bone alkaline phosphatase (ALP) from baseline to 4 weeks after the last injection and time to occurrence of SREs. Secondary end points included evaluation of safety, serum markers of bone turnover, PSA, and overall survival.

Sixty-four patients were enrolled from eleven centers in Sweden, Norway, and the UK: 33 patients were randomized to EBRT with ²²³Ra and 31 patients to EBRT with placebo.⁵¹ No difference in EBRT dose fractionation at baseline was observed between the groups. Hematological toxicity was minimal, with no thrombocytopenia observed in the ²²³Ra arm compared with one event in a placebo-arm patient. Grade ≥ 2 neutropenia occurred in three patients treated with ²²³Ra compared with none treated with placebo. No patient discontinued ²²³Ra because of treatment-emergent AEs, and there were more serious AEs in the placebo arm. The only statistically significant difference in AEs between the arms was constipation in twelve patients treated with ²²³Ra (mild–moderate in all but one case) versus two with placebo.

In addition to a tolerable safety profile, evidence of biologic effects and efficacy were demonstrated.⁵¹ The median change in bone ALP from baseline to 4 weeks after the last study injection was -65.6% in the ²²³Ra group compared with 9.3% in the placebo group ($P < 0.0001$). Median time to first

SRE was 14 weeks in the ²²³Ra arm versus 11 weeks in the placebo arm ($P = 0.257$), with a hazard ratio (HR) of 1.75 (95% confidence interval [CI], 0.96–3.19; $P = 0.065$) favoring ²²³Ra when adjusted for baseline covariates. The median relative change in PSA from baseline to 4 weeks after the last injection was -23.8% in the ²²³Ra group versus $+44.9\%$ in the placebo group ($P = 0.003$). Confirmed PSA responses by PSA Working Group criteria⁵³ ($\geq 50\%$ decline) were observed in eleven of 31 (35%) patients on the ²²³Ra arm and five of 28 (18%) on the placebo arm ($P = 0.153$), with median time to PSA progression of 26 weeks and 8 weeks, respectively, on each arm ($P = 0.048$). Notably, censoring for concomitant treatments did not substantially change the overall results. The median overall survival was 65.3 weeks for the ²²³Ra group versus 46.4 weeks for placebo ($P = 0.066$), with an adjusted HR of 2.12 (95% CI, 1.13–3.98; $P = 0.020$) favoring ²²³Ra. These survival results have been updated and remain similar with longer follow-up.⁵⁴ Post hoc analyses showed OS of all patients to be 102.4 versus 42.6 weeks ($P < 0.001$) for posttreatment normalized versus nonnormalized from baseline ALP values, respectively; patients on the ²²³Ra arm had OS of 102.1 versus 42.5 weeks ($P < 0.001$) for post-treatment normalized versus nonnormalized from baseline ALP values, respectively.⁵⁵ In summary, this randomized, placebo-controlled study showed that repeat dosing of ²²³Ra every 4 weeks is well tolerated in men with mCRPC and has a significant effect on bone ALP 4 weeks after finishing treatment, in addition to potential beneficial efficacy in terms of SREs, PSA, and overall survival end points.

The second study (BC1-03), a double-blind, randomized, dose-ranging study, was designed to examine the effect of a single injection of ²²³Ra at 5, 25, 50, or 100 kBq/kg in patients with progressive mCRPC and pain.⁵² Patients were required to have testosterone levels < 50 ng/dL after castration therapy, a score of ≥ 2 on the BPI,⁵⁶ progression of disease based on rising PSA levels, and sites of clinical pain correlating with multifocal osteoblastic disease on bone scintigraphy. The primary end point was the change in “pain index” (derived from a combination of the Visual Analogue Scale and analgesic consumption categorized according to the World Health Organization [WHO] analgesic ladder⁵⁷) at weeks 2, 4, 8, 12, and 16. Secondary end points included change from baseline in the BPI severity index and functional index, overall survival, duration of pain relief, relative change in bone ALP and PSA, and assessment of AEs.

One hundred patients were randomized and treated at 16 centers in Sweden, Germany, France, and the UK.⁵² Over half of patients had >20 bone lesions or a superscan,

81% had performance status of 0–1, 36% had prior docetaxel, and 48% had a baseline WHO level of analgesia of 3; median baseline Visual Analogue Scale was 42 mm. A statistically significant dose response for pain index was observed at week 2 only ($P = 0.035$). At week 8, the percentage of pain responders was 40%, 63%, 56% and 71% on the 5, 25, 50, and 100 kBq/kg arms, respectively. The BPI data also showed a significant dose response at week 8 for the Pain Severity Index ($P = 0.040$). In a post hoc analysis of pain responders, pain decreased by a mean of -30 , -31 , -27 , and -28 mm ($P = 0.008$, $P = 0.0005$, $P = 0.002$, and $P < 0.0001$). Furthermore, these responders showed an improvement in the BPI functional interference index in all groups. There were no differences in AEs among the dose groups, with the most frequent nonhematologic AEs being nausea, fatigue, vomiting, diarrhea, constipation, bone pain, urinary tract infection, and peripheral edema. In the two highest-dose groups, there appeared to be slightly greater reductions in platelet, leukocyte, and neutrophil counts. Nadir counts generally occurred at 2 weeks postinjection and subsequently returned to baseline. Changes in bone ALP were significant only in the 100-kBq/kg dose group at weeks 4 and 8 ($P < 0.0001$ and $P = 0.0067$, respectively), whereas PSA increased from baseline to week 16 in all dose groups. The median overall survival for the study population was 50 weeks and did not significantly differ among groups.

Overall, this study focusing on the pain-relieving effects of a single injection of ²²³Ra in escalating doses demonstrated an early dose response at week 2 and a maximum of 71% pain response at week 8 at the highest dose level. A well-tolerated safety profile was observed, although there were no effects on PSA levels and only a significant effect on bone ALP at the highest dose level. Notably, there may have been a problem with dropout bias, as 17 patients had dropped out by week 8 and there was differential dropout in the low- versus high-dose groups (eleven versus six patients).

A third randomized, double-blind dose-finding Phase II study of ²²³Ra (BC1-04) has only been reported in abstract form.^{54,57} Patients were randomized to 25, 50, or 80 kBq/kg every 6 weeks for 12 weeks (three total doses). The primary end point was PSA response ($\geq 50\%$ decline from baseline). Bone markers, SREs, AEs, and survival were also evaluated. Sixty-one percent of patients had an elevated ALP at baseline. In these patients, normalization of ALP was associated with a significantly better survival compared with those who did not have normalization of ALP.

Phase III study

The results of the international, randomized, double-blind Alpharadin in Symptomatic Prostate Cancer (ALSYMPCA) Phase III trial were recently presented.³⁵ Eligible patients had confirmed symptomatic CRPC, two or more bone metastases, no known visceral metastases, and were either docetaxel-pretreated or unfit for docetaxel. Patients were randomized 2:1 to either ²²³Ra injections at 50 kBq/kg with best standard of care or saline injections with best standard of care. Six injections were given at 4-week intervals. “Best supportive care” could include secondary hormonal therapies (antiandrogens, androgen biosynthesis inhibitors, steroids) or EBRT, but not cytotoxic chemotherapy or radioisotopes. Subjects were stratified according to total ALP, bisphosphonate use, and prior docetaxel treatment. The primary end point was overall survival, with secondary end points of time to first SRE, time to total ALP progression, total ALP response, total ALP normalization, time to PSA progression, safety, and quality of life. The trial was designed with 90% power to detect an HR of 0.76 with a two-sided alpha of 0.05. Data from a planned interim analysis after 314 events from 809 randomized patients were presented. The trial was stopped based on the recommendation of an independent data-monitoring committee, due to early evidence of benefit in terms of overall survival (predetermined boundary crossed).

From June 2008 through February 2011, the investigators randomized 541 patients to ²²³Ra and 268 patients to placebo (intention-to-treat group).³⁵ The baseline characteristics between the arms appeared well matched, with baseline Eastern Cooperative Oncology Group (ECOG) ≤ 1 in 86%, 6–20 metastases in 44%, and >20 metastases/superscan in 40%, and WHO ladder cancer pain index ≥ 2 in 54% on the ²²³Ra arm. About 58% had received prior docetaxel. Median total ALP was 213 $\mu\text{g/L}$, and PSA was 159 $\mu\text{g/L}$ on the ²²³Ra arm. Median overall survival was significantly improved in the ²²³Ra group compared with placebo: 14.0 versus 11.2 months (HR 0.695 [95% CI, 0.552–0.875]; $P = 0.00185$). In addition, time to first SRE was significantly improved in the ²²³Ra arm: 13.6 versus 8.4 months (HR 0.610 [95% CI, 0.461–0.807]; $P = 0.00046$). Significant improvements in the biochemical end points of time to total ALP progression (HR 0.163 [95% CI, 0.121–0.221]; $P < 0.00001$), time to PSA progression (HR 0.671 [95% CI, 0.546–0.826]; $P = 0.00015$), total ALP response (43% vs 3%; $P < 0.001$), and total ALP normalization (33% vs 1%; $P < 0.001$) were also observed.

Overall, ²²³Ra appeared to be quite well tolerated. Notably, there were fewer AEs in the ²²³Ra group than the placebo group as measured by all-grade AEs (88% vs 94%),

grade 3 or 4 AEs (51% vs 59%), serious AEs (43% vs 55%), and discontinuation due to AEs (13% vs 20%). The incidence of grade 3 or 4 neutropenia in the ^{223}Ra group was 2% versus 1% in the placebo arm. Grade 3 or 4 thrombocytopenia was observed in 4% of subjects on the ^{223}Ra arm versus 2% on the placebo arm. All-grade AEs and grade 3 or 4 anemia were similar between arms. In terms of all-grade nonhematologic AEs, diarrhea (22% vs 13%) and vomiting (17% vs 13%) appeared to be more frequent in the ^{223}Ra group, whereas nausea (34% vs 32%) and constipation (18% vs 18%) appeared similar between groups.

Subgroup analysis demonstrated survival benefits across most clinically important patient subgroups, regardless of current use of bisphosphonates, prior use of docetaxel, or ECOG performance status.³⁵ One interesting result was that the HR appeared better in patients currently using bisphosphonates compared with those not on bisphosphonates. There is some biologic rationale for this effect, since the mechanism of action for bisphosphonates is inhibition of osteoclast activity.⁵⁹ In theory, this decreased osteoclastic activity could result in ^{223}Ra having increased effect at sites of osteoblastic activity, due to longer binding times.³⁵ It remains to be seen whether this effect would also be seen with denosumab, a monoclonal antibody against RANKL, but one might expect similar results. It would also be interesting to evaluate ^{223}Ra with agents known to elicit osteoblastic responses on bone scan, such as abiraterone acetate.⁶⁰

More detailed results of the impact of ^{223}Ra on SREs were presented recently as well.⁶¹ In contrast to other trials of bone-targeted agents,¹⁶ no skeletal surveys were routinely performed during the ALSYMPCA trial; all imaging was performed only as clinically indicated.³⁵ SRE components included pathologic bone fracture, spinal cord compression, EBRT, and surgical intervention. In addition to delaying time to first SRE (as mentioned above), ^{223}Ra significantly delayed time to all SRE components except surgical intervention.⁶¹ EBRT was the most common SRE component: 23% vs 27% for the ^{223}Ra and placebo arms, respectively (HR 0.65 [95% CI, 0.48–0.87]; $P = 0.0038$). Pathologic bone fracture was observed in 4% vs 7%, respectively (HR 0.45 [95% CI, 0.24–0.86]; $P = 0.013$). Of particular interest, spinal cord compression occurred in 3% of patients on the ^{223}Ra arm compared with 6% on placebo (HR 0.44 [95% CI, 0.22–0.88]; $P = 0.016$). Although not common, this dreaded complication results in significant morbidity in men with advanced prostate cancer.⁶² This is the first study to demonstrate a significant effect on delay of spinal cord compression in this population.

At the time of this writing, no quality-of-life or pain-response data from the ALSYMPCA trial have been reported. Ideally, a therapy that prolongs OS and delays SREs, besides having biochemical effects, should do so with minimal compromise of quality of life and with improvements in pain. These results are eagerly awaited in order to confirm the benefit of ^{223}Ra in terms of patient-reported outcomes.

Critical appraisal and potential role of ^{223}Ra in therapy of mCRPC

The pivotal Phase III randomized double-blind placebo controlled ALSYMPCA trial of ^{223}Ra demonstrated a highly significant OS improvement in docetaxel-pretreated or docetaxel-unfit men with symptomatic bone-metastatic CRPC and a very tolerable side-effect profile. A large number of men in the US with mCRPC are unfit for systemic chemotherapy due to toxicity concerns or comorbidities, and many men with mCRPC decline chemotherapy and all eventually fail first-line docetaxel. ^{223}Ra is pending regulatory approval in the US and abroad; however, based on recent FDA approvals in mCRPC based on overall survival benefits,^{5,12–14} approval of ^{223}Ra appears likely. Although time to first SRE was not the primary end point of the ALSYMPCA trial, the effects of ^{223}Ra on delaying SREs are important, and this end point has led to the regulatory approval of other bone-targeted agents even in the absence of beneficial effects on overall survival and disease progression.^{15,16} Based on eligibility criteria from this pivotal trial, it is likely that the label will be broad, encompassing both men with symptomatic bone-metastatic CRPC who have failed docetaxel and those who are not candidates for docetaxel chemotherapy.

The population of the ALSYMPCA trial was defined somewhat differently compared with prior trials in mCRPC. Because docetaxel/prednisone was the first therapy proven to extend survival in men with mCRPC and therefore became the first-line standard of care, many contemporary trials have focused on either “pre-docetaxel” or “post-docetaxel” populations. More recent trials have also focused on “asymptomatic or minimally symptomatic” patients (eg, IMPACT,¹² COU-AA-302,⁶³ PREVAIL⁶⁴). However, this is the first Phase III study of a survival-prolonging therapy to concentrate on the symptomatic, bone-metastatic subpopulation of mCRPC patients. Therefore, ^{223}Ra represents a unique treatment option in this subgroup. ^{223}Ra occupies a unique niche in that it prolongs OS, is a bone-targeted agent that delays SREs, and is also a radiopharmaceutical that might be expected to provide pain palliation (Phase III data not yet reported).

²²³Ra has not been compared head-to-head against other approved therapies in mCRPC. However, with this caveat and based on what is known from the fairly extensive study of ²²³Ra in this population to date, the following observations can be made.

Efficacy of ²²³Ra

- A large and significant improvement in OS was observed when compared with placebo in men with mCRPC and symptomatic bony metastases. The concurrent demonstration of benefit in terms of delayed SREs and improvement in all biochemical end points (ie, PSA, total ALP), which would be expected with a therapy of ²²³Ra's mechanism of action, adds to the robustness of this finding.
- Subgroup analysis demonstrates that OS improvement was consistent across multiple clinically relevant subgroups. Importantly, these benefits were seen in prespecified groups (strata), including total ALP < 220 U/L and ≥220 U/L; current bisphosphonate use (yes/no); or prior use of docetaxel (yes/no).
- The population of patients in the ALSYMPCA trial included both docetaxel-unfit and docetaxel-pretreated men. This makes cross-trial comparisons more difficult, since eligibility criteria for trials in mCRPC have historically focused on either chemo-naïve or chemo-pretreated populations. Men who are unfit for docetaxel-based chemotherapy may have a poorer survival relative to those who are chemotherapy candidates.⁶⁵
- The reason for the choice of treatment with six total injections (or until progression of disease) is not clear, and could be an area for future study.
- Overall survival (Table 1):
 - Cytotoxic chemotherapy: The absolute median OS difference of 2.8 months observed on the ALSYMPCA trial compares favorably with the 2.9-month difference seen in the chemo-naïve (but docetaxel-fit) population in the TAX-327 study⁶⁶ and the 2.4-month difference in the docetaxel-pretreated population in the TROPIC study.¹³ However, it should be noted that both of these latter two trials used an active comparator (mitoxantrone plus prednisone¹⁰).
 - AR-directed therapies: Trials with androgen receptor (AR)-directed therapies, such as abiraterone¹⁴ and MDV3100,¹⁷ in docetaxel-pretreated populations have demonstrated median OS differences of 4.6 and 4.8 months, respectively. Notably, these trials used the less active comparator of placebo plus prednisone. However, there is a strong rationale for combining these agents with ²²³Ra based on the allowance of these classes of agents in the ALSYMPCA trial and the non-overlapping toxicity profiles. Therefore, evaluation of combination versus sequential therapy with these agents should be encouraged.
 - Radiopharmaceuticals: None of the currently FDA-approved radiopharmaceuticals (eg, ⁸⁹Sr, ¹⁵³Sm) have demonstrated an OS benefit in a randomized Phase III study in men with mCRPC.¹¹
 - Antiresorptive agents: None of the currently FDA-approved osteoclast inhibitors (eg, zoledronic acid, denosumab) have demonstrated OS benefits over placebo. However, their use with ²²³Ra is likely to be beneficial without overlapping toxicity based on the Phase III evidence to date.
- Skeletal-related events (Table 4):
 - Cytotoxic chemotherapy: There is insufficient evidence to demonstrate that docetaxel and cabazitaxel prevent or delay SREs, although they are known to result in pain palliation and to prolong time to pain progression, disease progression, and overall survival.
 - AR-directed therapies: Abiraterone has demonstrated delay in time to first SRE (25th percentile, 301 vs 150 days; *P* < 0.0001) in the COU-AA-301 trial.²⁰ Time to first SRE was a secondary end point in the

Table 4 Skeletal-related event (SRE) delay in recent Phase III trials of bone-targeted therapies in bone-metastatic mCRPC

Agent (trial, year)	Mechanism of action	Disease state	Comparator	Hazard ratio	Time to 1st SRE, months (P-value)
Zoledronic acid (Zometa 039, 2002) ¹⁵	Bisphosphonate – osteoclast inhibitor	BM mCRPC, asymptomatic	Placebo	0.80	13.8 vs 10.6 (0.02)
Denosumab (2010) ¹⁶	RANK-L antibody – osteoclast inhibitor	BM mCRPC, asymptomatic	Zoledronic acid	0.82	20.7 vs 17.1 (0.008)
Radium-223 (ALSYMPCA) ³⁵	Radiopharmaceutical – calcium mimic	BM mCRPC, symptomatic	Placebo + BSC*	0.61	13.6 vs 8.4 (0.00046)

Note: *BSC included secondary hormonal therapies, external beam radiotherapy, and bisphosphonates (41%), but not cytotoxic chemotherapy or radiopharmaceuticals.
Abbreviations: BM, bone-metastatic; mCRPC, metastatic castrate-resistant prostate cancer; BSC, best supportive care.

AFFIRM trial of MDV3100 (NCT00974311), but this result has not yet been reported.¹⁷

- Radiopharmaceuticals: There is insufficient evidence to demonstrate that ⁸⁹Sr or ¹⁵³Sm prevent or delay SREs.¹¹
- Antiresorptive agents: Zoledronic acid delays SREs compared with placebo, and denosumab is superior to zoledronic acid in delaying SREs in men with mCRPC. Notably, subgroup analysis of the ALSYMPCA trial suggested that bisphosphonates may potentiate the activity of ²²³Ra; a similar effect would be expected with denosumab, though there is a lack of data regarding this.
- Pain palliation was demonstrated in Phase III trials of docetaxel and abiraterone, but not cabazitaxel (Table 2). A key indication for the use of radioisotopes for men with mCRPC has been pain palliation, although there is likely only a small benefit in complete reduction of pain over 1–6 months and no increase in analgesic use (Table 5).¹¹ Data on pain palliation from the ²²³Ra Phase III ALSYMPCA trial have not been reported; however,

the Phase I and II experience with ²²³Ra would suggest a benefit in terms of pain palliation.

Safety and toxicity profile

- The most common nonhematologic side effects of ²²³Ra in the ALSYMPCA trial include diarrhea, nausea, vomiting, and constipation. Notably, nausea and constipation did not appear to be more frequent on the ²²³Ra arm versus placebo. Two percent or fewer of these nonhematologic, gastrointestinal side effects were grade 3 or 4. Overall, only about 10% of patients on the ²²³Ra arm had grade ≥ 3 AEs, fewer than on the placebo arm.
- Neutropenia and thrombocytopenia are side effects of ²²³Ra and occurred overall in 4% and 8%, respectively, of patients in the ALSYMPCA trial. Grade 3 or 4 neutropenia and thrombocytopenia were observed in 2% and 4%, respectively.
- In contrast with other radioisotopes, ²²³Ra appears to have much less myelosuppression. This property allows consecutive doses to be administered safely, and may be the basis for its more substantial antitumor effects and

Table 5 Radiopharmaceuticals in selected randomized trials in men with prostate cancer

Trial, dose	Comparator	Overall survival	Pain palliation	Key side effects	Comments
Strontium-89					
Canadian 400 MBq × 1 adjunct to RT (n = 126) ²⁵	Placebo	No difference	No difference	Increased hematologic toxicity with ⁸⁹ Sr	Differences in pain progression, PSA, ALP, QoL favoring ⁸⁹ Sr
British 200 MBq × 1 (n = 284) ²⁶	EBRT (F or HB)	No difference*	No difference†	↓WBC and ↓PLT by 30%–40% with ⁸⁹ Sr	RT to new site less frequent with ⁸⁹ Sr (P < 0.01)
EORTC 150 MBq × 1 (n = 203) ²⁷	Local field RT	RT superior vs ⁸⁹ Sr‡	No difference§	No difference between groups	No difference in PFS or TTP; PSA responses in 10%–13%
Samarium-153					
Serafini et al 0.5 or 1.0 mCi/kg × 1 (n = 118; 68% PC) ²⁸	Placebo	No difference	Only with 1.0 mCi/kg dose¶	Mean WBC and PLT nadirs 3100/μL and 118,000/μL with 1.0 mCi/kg¶	72% and 43% pain relief at 4 and 12 weeks with 1.0 mCi/kg
Sartor et al 1.0 mCi/kg × 1 (n = 152) ²⁹	Placebo	No difference	Significant reduction within 1–2 weeks lasting to 4 weeks**	Mean WBC and PLT nadirs 3800/μL and 127,000/μL with ¹⁵³ Sm††	Significant reductions in opioid use at 3 and 4 weeks with ¹⁵³ Sm; retreatment feasible ²⁹
Radium-223					
ALSYMPCA 50 kBq/kg × 6 (n = 809) ³⁵	Placebo	14.0 vs 11.2 months (P = 0.00185)	Not reported	Diarrhea, vomiting; grade ≥ 3 ANC (2%) and PLT (4%)	Significant delay in SREs ⁵⁸ and improvements in PSA and ALP

Notes: *33 vs 28 weeks for ⁸⁹Sr vs RT (P = 0.1); †sustained relief in two-thirds at 12 weeks, all 3 treatments provided similarly effective pain relief; ‡11 vs 7 months for RT vs ⁸⁹Sr (P = 0.0457); §subjective response in about one third, no difference in subjective pain response between groups, compared with placebo, significant pain reductions at 1.0 mCi/kg, but not 0.5 mCi/kg, at 1 and 4 weeks; ¶compared with placebo, significant pain reductions at 1.0 mCi/kg, but not 0.5 mCi/kg, at 1 and 4 weeks; ††no grade 4 hematologic toxicity observed, complete recovery of myelosuppression by 8 weeks; **placebo-treated patients could cross over to receive ¹⁵³Sm after 4 weeks; ††counts generally recovered by 8 weeks.

Abbreviations: MBq, megabecquerel; RT, radiotherapy; PSA, prostate-specific antigen; ALP, alkaline phosphatase; QoL, quality of life; EBRT, external beam radiotherapy; F, focal; HB, hemibody; ⁸⁹Sr, strontium-89; EORTC, European Organization for Research and Treatment of Cancer; PFS, progression-free survival; TTP, time to progression; mCi, millicurie; PC, prostate cancer; ANC, absolute neutrophil count; PLT, platelets; SRE, skeletal-related event.

OS compared with β -emitters. Additionally, with ²²³Ra, neutropenia predominates over thrombocytopenia, which is the inverse of the pattern seen with β -emitters.

- Judged against cytotoxic chemotherapies, ²²³Ra is likely to have a significantly better toxicity profile in terms of myelosuppression and gastrointestinal and other side effects. In an extreme example, in the TROPIC trial of cabazitaxel, grade 3 or 4 diarrhea was observed in 6.2% and grade 3 or 4 neutropenia in 81.7% (febrile neutropenia 7.5%).
- In comparison to AR-directed therapies, ²²³Ra has a distinct toxicity profile but may be similarly tolerable. Patients treated with abiraterone acetate have demonstrated side effects related to mineralocorticoid excess due to the drug's mechanism of action, such as fluid retention, hypertension, and hypokalemia.¹⁴ The most common side effect overall and grade 3 or 4 side effect observed with MDV3100 was fatigue, with patients rarely experiencing seizures (0.6%; all grade ≥ 3).¹⁷
- Antiresorptive agents are likely to be used in combination with ²²³Ra, as in the Phase III trial, and side effects generally appear to be nonoverlapping.
- Data on quality of life with ²²³Ra from the ALSYMPCA trial are eagerly awaited.
- In comparison to β -emitters, which are renally excreted, ²²³Ra is eliminated via the small intestine. This could be an important advantage in patients with mCRPC.
- Long-term safety data with ²²³Ra are lacking. However, there is extensive experience with ²²⁴Ra in patients with ankylosing spondylitis.⁴² An increased risk for later cancers has been observed, but only in individuals treated with ²²⁴Ra as children and, importantly, not in those treated as adults.⁶⁷ In comparison, there have been reports of acute leukemia with ⁸⁹Sr but not ¹⁵³Sm.⁶⁸

Future directions

Emerging therapies aimed at preventing skeletal morbidity in men with prostate cancer have recently been reviewed in detail.⁶⁹ Notable bone-targeted therapies in clinical development for mCRPC include SRC-targeted therapies (dasatinib), and MET-targeted therapies. While the oral endothelin (ET-A) receptor antagonists atrasentan and zibotentan (ZD4054) were not successful in Phase III trials when combined with docetaxel in mCRPC, it is possible that these agents may combine favorably with other bone-targeted strategies. The oral SRC tyrosine kinase inhibitor dasatinib (Sprycel; Bristol-Myers Squibb, New York, NY) is being evaluated in a Phase III mCRPC trial of docetaxel/prednisone with dasatinib or placebo (NCT00744497),⁷⁰ with results anticipated in 2012.

Finally, the multitargeted tyrosine kinase inhibitor XL-184 (cabozantinib), which inhibits MET, VEGFR2, RET, and Kit, has shown impressive results in a Phase II study⁷¹ and will enter Phase III testing soon.^{72,73}

Beta emitters have been combined with chemotherapy in several studies, including two randomized studies, demonstrating the possible feasibility and safety of this approach.^{31–34} For example, one recent Phase I study by Morris et al demonstrated that docetaxel and ¹⁵³Sm could be administered at full doses over repeated cycles.³¹ Given the improved toxicity profile with ²²³Ra over β -emitters, it seems likely that ²²³Ra could be combined with chemotherapy as well. This concept is currently being investigated in a Phase I/II trial of ²²³Ra with docetaxel chemotherapy in men with bone metastasis from CRPC (NCT01106352).⁷⁴ As a synergistic interaction between androgen-deprivation therapy and radiotherapy that increases apoptosis is known to exist in prostate cancer,⁷⁵ it is conceivable that this synergy could exist between ²²³Ra and the newer AR-directed therapies (eg, abiraterone, MDV3100) as well. Finally, it is possible that ²²³Ra and bone-targeted agents in development could have complementary mechanisms of action. All of these remain important research questions that should be addressed in the near future.

Conclusion

The overall risk-to-benefit ratio of ²²³Ra appears quite favorable. The available data demonstrate that ²²³Ra has activity in men with symptomatic bone-metastatic CRPC who are either docetaxel-unfit or docetaxel-pretreated. The significant improvement in median OS is an acceptable surrogate of clinical benefit, and is bolstered by delay of SREs and improvement in biochemical end points. These benefits are in the range observed with other approved therapies in this setting. When examined in the context of ²²³Ra-associated toxicity, these benefits appear well worth the risk in the subpopulation of patients included in the ALSYMPCA trial. Side effects were mild and predominantly gastrointestinal (diarrhea and vomiting). Myelosuppression was minimal, with rare grade ≥ 3 neutropenia and thrombocytopenia. Toxicities appear to be less than those with cytotoxic chemotherapies and are similarly mild, though distinct, when compared to AR-directed therapies. Significantly less myelosuppression is observed with ²²³Ra compared with β -emitters. The effects of ²²³Ra on quality of life and pain palliation from the randomized Phase III trial have not been reported. In clinical practice, it is likely that ²²³Ra would be used in conjunction with antiresorptive agents. Compared

with approved cytotoxic chemotherapies, AR-directed therapies, and other radioisotopes, ^{223}Ra could occupy a unique niche in the treatment of mCRPC.

Disclosure

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