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INVITED REVIEW

Prostate Cancer

Bone-targeted therapies to reduce skeletal morbidity in prostate cancer

Tanya B Dorff[1], Neeraj Agarwal[2]

Bone metastases are the main driver of morbidity and mortality in advanced prostate cancer. Targeting the bone microenvironment, a key player in the pathogenesis of bone metastasis, has become one of the mainstays of therapy in men with advanced prostate cancer. This review will evaluate the data supporting the use of bone-targeted therapy, including (1) bisphosphonates such as zoledronic acid, which directly target osteoclasts, (2) denosumab, a receptor activator of nuclear factor-kappa B (RANK) ligand inhibitor, which targets a key component of bone stromal interaction, and (3) radium-223, an alpha-emitting calcium mimetic, which hones to the metabolically active areas of osteoblastic metastasis and induces double-strand breaks in the DNA. Denosumab has shown enhanced delay in skeletal-related events compared to zoledronic acid in patients with metastatic castration-resistant prostate cancer (mCRPC). Data are mixed with regard to pain control as a primary measure of efficacy. New data call into question dosing frequency, with quarterly dosing strategy potentially achieving similar effect compared to monthly dosing for zoledronic acid. In the case of radium-223, there are data for both pain palliation and improved overall survival in mCRPC. Further studies are needed to optimize timing and combination strategies for bone-targeted therapies. Ongoing studies will explore the impact of combining bone-targeted therapy with investigational therapeutic agents such as immunotherapy, for advanced prostate cancer. Future studies should strive to develop biomarkers of response, in order to improve efficacy and cost-effectiveness of these agents.
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INTRODUCTION

Osseous metastases are a hallmark of advanced prostate cancer and define the majority of the morbidity patients with this disease experience. Skeletal-related events (SREs) are typically defined as fractures, bone pain requiring radiation, and spinal cord compression. With the introduction of bisphosphonates, a two-pronged approach emerged for the management of metastatic castration-resistant prostate cancer (mCRPC) patients: treatment targeted at the cancer cells and treatment targeted at the microenvironment. The field has now expanded to include receptor activator of nuclear factor-kappa B (RANK) ligand inhibition. The use of radiopharmaceuticals for palliation of bone pain from metastatic disease has evolved with the availability of radium-223, which was found to prolong overall survival in addition to reducing SREs. Additional agents targeting endothelin, Src, and c-Met have not come into clinical practice. We will review elements of the unique interaction between prostate cancer and the bone microenvironment, with an emphasis on therapeutic implications and areas of ongoing research. A summary of bone-targeted agents and their mechanism of action is presented in **Figure 1**.

PROSTATE CANCER AND THE BONE MICROENVIRONMENT

Our understanding of the mechanisms for prostate cancer affinity for the bone is limited, but molecules such as integrins,[1] cathepsin,[2] and RANK-ligand[3] have been implicated in the homing and invasion of prostate cancer cells into the bone. Integrins are key regulators of processes which facilitate growth of cancer cells in a new environment, and upregulation of the α_v-integrin has been identified as one critical change in prostate cancer metastases to bone, reviewed by Goel *et al.*[4] This has led to therapeutic targeting of integrins, including agents such as cilengitide, which inhibits $\alpha_v\beta_3$ and $\alpha_v\beta_5$ subunits,[5] as well as antibodies including intetumumab[6] and MEDI-522.[7] Challenges in clinical development of integrin-targeted therapy include rational and feasible clinical trial design to prevent bone metastases as these agents may have less impact on established tumors. Once arrived in the bone, proteases such as cathepsin and matrix metalloproteinases facilitate invasion;[2,8] targeting these processes has been promising preclinically,[9] but human translational studies are lacking. RANK-ligand then becomes critical in the harnessing of the normal bone turnover machinery to promote prostate cancer growth. Normally expressed on osteoclasts and important for osteoclast differentiation and proliferation, the expression of RANK-ligand and osteoprotegerin, which can signal via the RANK pathway, on prostate cancer cells has been associated with metastatic burden and aggressive behavior.[3,9,10] The importance of this pathway is highlighted by the development of denosumab, a human monoclonal antibody against RANK-ligand, reviewed by Lacey *et al.*[11]

However, there is also clearly a role of the "soil" as a permissive environment which is not only receptive to, but promotes prostate cancer growth in the bone. Osteoblast precursors and osteoclasts, as

[1]USC Keck School of Medicine, USC Norris Comprehensive Cancer Center, Genitourinary Oncology, Los Angeles, CA 90033, USA; [2]Hunts Man Cancer Institute, University of Utah, 2000 Circle of Hope, Salt Lake City, UT 84112, USA.
Correspondence: Dr. TB Dorff (dorff@usc.edu)
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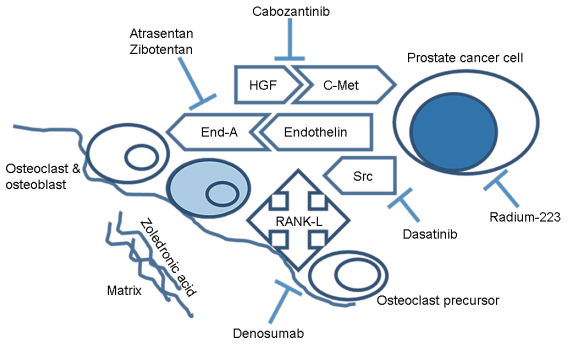

Figure 1: Summary of targets for bone–prostate cancer interaction and therapeutic agents. HGF: hepatocyte growth factor. End-A: Endothelin-A receptor; RANK-L: receptor activator of nuclear factor-kappa B ligand.

well as vasculature and other components of the endosteal surface, contribute to proliferation or dormancy in addition to the tumor cell-expressed factor contributions. This complex interaction is reviewed by Croucher *et al*.[12] Subsequently, prostate cancer cells influence the osteocytes and induce supportive changes for prostate cancer growth, by a variety of mechanisms including physical pressure by cancer cells on osteoblasts,[13] secretion of prostate acid phosphatase,[14] secretion of endothelin-1[15] and secretion of exosomes which promote increased pyruvate kinase M2 (PKM2) expression, and ketone production.[16]

Using signals such as TGFβ and IL6, prostate cancer cells cause excess remodeling by osteoblasts and osteoclasts, reviewed by Eaton and Coleman.[17] Although prostate cancer metastases most commonly have an osteoblastic appearance radiographically, there is typically a component of osteolysis, and there is an increased risk of fracture. Not all bone metastases are associated with pain, but there is some correlation with elevated N-telopeptide levels or serum calcium levels and presence of pain related to bone metastsases,[18] and it is common in patients with metastatic prostate cancer. Interfering with the various aspects of prostate cancer homing to bone and potentiating interactions with the microenvironment is clearly a high priority for reducing prostate cancer progression, but importantly also can be expected to reduce these destructive changes which produce complications including pain and fractures.

BONE-TARGETED THERAPIES

Bisphosphonates

Bisphosphonates have high affinity for hydroxyapatite and concentrate near osteoclasts, where bone mineral is exposed. They are thought to mediate their effect via direct actions on osteoclasts, such as interfering with adhesion, recruitment, cytoskeleton arrangement, differentiation, and survival.

The bisphosphonate zoledronic acid has been shown to be effective in reducing the risk of SREs. In a landmark trial, men with castration-resistant prostate cancer and osseous metastases were randomized to receive 4 mg or 8 mg of zoledronic acid or placebo intravenously (IV) every 3 weeks. The 8 mg dose caused excess renal toxicity and was switched to 4 mg during the study conduct; in total, 214 men received 4 mg, 221 received 8 mg (subsequently reduced to 4 mg; 8 mg/4 mg), and 208 received placebo. Treatment with zoledronic acid resulted in an 11% absolute risk reduction for skeletal events, as well as a significant delay in the time to development of a skeletal event ($P = 0.009$).[19] Skeletal events were defined as pathological fracture, spinal cord compression, additional surgery or radiotherapy to bone, or change in antineoplastic therapy in order to control bone pain. There were trends toward improved quality of life and lower rates of increasing pain scores during treatment, but they did not reach statistical significance.

A cost-effectiveness analysis revealed that, despite fewer events and hospitalization days, the expense per quality-adjusted life-year saved ($159 200) was greater than generally held standards.[20] Nevertheless, there was robust clinical uptake of zoledronic acid by the prostate cancer community. Cost-effectiveness would improve if a less intense treatment schedule could similarly reduce SREs. The initial dosing of every 3–4 weeks for zoledronic acid matched chemotherapy dosing, in an era of docetaxel being the main treatment for mCRPC. Dosing was also based on kinetics of bone turnover markers such as urine N-telopeptide; markers were noted to decline after dosing, then begin to rise typically within 4 weeks in patients with bone metastases.[21] While urine N-telopeptide was proven to have prognostic significance for survival in men with advanced prostate cancer,[22] treatment kinetics were not necessarily linked to skeletal outcomes. Two recent studies have now called into question the 4-week dosing schedule of zoledronic acid. The OPTIMIZE-2 trial found that every 12 weeks dosing of zoledronic acid achieved similar control of skeletal morbidity compared to the standard schedule of every 4 weeks dosing in breast cancer patients with bone metastases.[23] A second study including 1822 patients with breast or prostate cancer, or multiple myeloma, also found noninferiority of 12-week dosing.[24] There was less control of telopeptide level with the longer dosing interval. Interestingly, neither trial noted a lower rate of toxicity. Nevertheless, these trials form a compelling rationale to dose zoledronic acid less frequently (*i.e*., every 12 weeks) since the primary outcome of SRE control is not compromised.

In vitro data show that bisphosphonates interfere with the adhesion of cancer cells to the bone matrix, and other microenvironment changes which might prevent the development or progression of bone metastases.[25] However, in castration-sensitive metastatic prostate cancer, early zoledronic acid did not seem to have enhanced impact. The Cancer and Leukemia Group B (CALGB) 90202 trial[26] testing this hypothesis was terminated early after the sponsor withdrew financial support, with 625 men (of planned 680 targets) randomized. The study failed to reach its primary end point; there was no significant difference in time to SRE which occurred at a median of 31.9 months for patients receiving zoledronic acid and 28.8 months for placebo (hazard ratio [HR]: 0.97, 95% confidential interval [CI]: 0–1.174; stratified log-rank $P = 0.385$). However, the subset of men with prior SRE had a nearly significant reduction in second SRE, median 31.9 months for zoledronic acid compared to 17.6 months for placebo, $P = 0.054$. This provides some rationale for selected application of zoledronic acid early, for patients at the highest risk of skeletal morbidity. Furthermore, in the Systemic Therapy in Advanced or Metastatic Prostate Cancer: Evaluation of Drug efficacy (STAMPEDE) study, which included 593 men with nonmetastatic prostate cancer randomized to standard of care (SOC) plus zoledronic acid, no improvement in disease progression or overall survival (HR: 0.95, 95% CI: 0.79–1.15; $P = 0.613$) was noted.[27] Thus, the indication for adding zoledronic acid or denosumab to treat bone metastases remains in the setting of castration-resistant disease.

In the CALGB trial, patients were advised to take calcium plus Vitamin D. The dose of zoledronic acid was reduced for renal insufficiency (3.5 mg for creatinine clearance of 50–60 ml min^{-1}, 3.3 mg for creatinine clearance 40–49 ml min^{-1}, and 3.0 mg for creatinine clearance of 30–39 ml min^{-1}), and persistent increases in serum creatinine >4 weeks resulted in treatment discontinuation. These

management strategies are important for all clinicians prescribing zoledronic acid for prostate cancer patients with bone metastases. In addition, it is important to note that pain palliation has not been consistently identified in placebo-controlled trials of bisphosphonates,[28] although pain requiring radiation is a SRE included in the registrational trial end point definition. Thus, pain management with analgesics and radiation should be utilized as indicated during the initiation of bisphosphonate therapy.

Denosumab

RANK ligand is a final common pathway in bone stromal interaction, with potent impact on recruitment, differentiation, and proliferation of osteoclasts.[8] Denosumab, a human antibody against RANK ligand, was developed to interfere with excessive bone remodeling, both for osteoporosis and osseous metastasis. A randomized trial compared monthly subcutaneous denosumab (120 mg) to monthly intravenous zoledronic acid (4 mg) in 1904 men with mCRPC and osseous involvement. Calcium plus vitamin D supplementation was strongly encouraged. Median time to SRE was 20.7 months for denosumab compared to 17.1 months for zoledronic acid, with a HR of 0.82 (95% CI: 0.71–0.95), $P = 0.008$ for superiority analysis.[29] Hypocalcemia was more common with denosumab (13% compared to 6% for zoledronic acid, $P < 0.0001$), and acute-phase reactions were more common with zoledronic acid (18% compared to 8% for denosumab), but discontinuation due to adverse reaction was similar (15% for zoledronic acid and 17% for denosumab). Osteonecrosis of the jaw (ONJ) incidence was similar, 2% for denosumab and 1% for zoledronic acid ($P = 0.09$), and associations with poor oral hygiene, dental extraction, dental appliance use, and concurrent chemotherapy were noted.[29]

Due to the role of RANK ligand in the development of bone metastases, interest in using denosumab as a preventive strategy led to clinical trials in castration-resistant nonmetastatic (biochemically recurrent) prostate cancer. Compared to placebo, a delay in time to bone metastasis was noted with denosumab, but with 1342 men randomized, there was no difference in progression-free or overall survival.[30] A subset analysis of men with rapid prostate-specific antigen (PSA) doubling time (<10 months) did identify an advantage; time to first bone metastasis was 32.4 months versus 26 months (HR: 0.85, 95% CI: 0.71–1.01).[31] Regulatory approval for use of denosumab in the prevention setting has not been obtained. However, the dose for osteopenia (60 mg subcutaneously every 6 months) is applicable to men with nonmetastatic or castration-sensitive metastatic disease who are receiving long-term androgen deprivation therapy as this was shown to reduce the incidence of vertebral fractures.[32]

Endothelin-A antagonists

Endothelin is commonly produced by prostate cancer cells, and signaling through the endothelin-A receptor leads to increased osteopontin and osteocalcin secretion, decreased osteoclastic bone resorption, and hence favors bone formation.[33] Together with signaling through other growth factor pathways, this promotes osteoblastic tumor formation. This led to interest in studying endothelin antagonists in prostate cancer. Atrasentan was developed as an oral endothelin-A antagonist and was found to suppress bone turnover in men with metastatic prostate cancer to the bone in a randomized, placebo-controlled trial.[34] Single-agent, randomized placebo-controlled study of 809 patients with mCRPC identified a trend toward delayed time to disease progression but was not statistically significant, despite evidence of biologic impact on bone turnover.[35] A second randomized controlled trial of atrasentan, in combination with docetaxel (SWOG S0421), also failed to meet its co-primary end points of progression-free and overall survival.[36] Zibotentan, a second endothelin-A antagonist, underwent similar testing with similar results. A phase III randomized trial of single-agent zibotentan added to prostate cancer treatment in 594 men with mCRPC did not prolong survival, despite the signal seen in earlier testing.[37] A phase III randomized trial found no benefit to adding zibotentan to docetaxel chemotherapy for mCRPC.[38] A randomized trial in nonmetastatic (biochemically recurrent) prostate cancer was halted at interim analysis due to likely failure to meet the co-primary end points of overall survival and progression-free survival.[39] Subsequent development of agents targeting this pathway has been limited.

Src inhibitors

Src is a signaling pathway with multiple effects on carcinogenesis and cancer cell survival, most intriguingly having been linked with delayed activation of dormant bone metastases in breast cancer.[40] Encouraging results in animal models led to several clinical studies of Src inhibition in prostate cancer. AZD0530 was studied in mCRPC by the California Cancer Consortium, but there were only five transient PSA responses in 28 patients and relatively short progression-free survival of 8 weeks though the definition included PSA-based progression which may have limited the assessment of the treatment impact.[41] Dasatinib was studied in a similar study but with broader end points including markers of bone turnover, which suggested that Src inhibition resulted in reduced bone turnover.[42] Unfortunately, a randomized placebo-controlled phase III study of docetaxel alone or in combination with dasatinib found no improvement in overall survival although there was a trend toward delayed time to SRE and PSA progression.[43] There was similarly no clear improvement in progression-free survival in a randomized study of abiraterone alone or with dasatinib.[44] Further study may be indicated with alternative agents or in earlier phase of the disease, given the mechanism by which Src signaling is thought to promote prostate cancer progression.

c-Met inhibitors

The finding that the Met receptor is overexpressed frequently in prostate cancer, especially in bone metastases, potentially induced by growth factors including hepatocyte growth factor (HGF) in the bone microenvironment,[45] led to interest in studying Met inhibition in prostate cancer. Cabozantinib, a receptor tyrosine kinase inhibitor of vascular endothelial growth factor (VEGF) and MET, initially showed strong activity in prostate cancer, with dramatic effects on bone scan including 12% complete resolution as well as 67% reduction in bone pain and significant declines in bone turnover markers in 57%.[46] Unfortunately, in a randomized study, cabozantinib failed to prolong survival compared to placebo (HR: 0.9, 95% CI: 0.76–1.06) despite delayed radiographic progression-free survival (HR: 0.48, 95% CI: 0.4–0.57), SREs, and evidence of circulating tumor cell conversion supporting efficacy.[47] Further study may be warranted in an enriched population if a selection biomarker could be identified.

RADIOPHARMACEUTICALS

Samarium, strontium

Calcium mimetic beta-emitting radiopharmaceuticals such as samarium 125-lexidronate and strontium-89 provide important palliative benefit for men with multiple sites of bone pain.[25] Pain palliation is rapid; with samarium-153 onset of pain relief occurred in 76% of patients within 4 weeks, and associated in 32% of cases with discontinuation of

opioid medications.[26] Grade 3 or 4 hematologic toxicity is modest at the 1 mCi kg^{-1} dose with 10% grade 3–4 neutropenia and 10% grade 3–4 thrombocytopenia. Similarly, with strontium-89, there was 78% pain palliation, with better responses noted in patients with <10 bone metastases compared to those with more extensive bone metastases.[27] Grade 3–4 neutropenia was noted in 1% of patients and grade 3–4 thrombocytopenia in 5% of patients, with a nadir at 4–6 weeks. In the case of both agents, repeated doses have been administered safely and increased the duration of pain relief. Phase II data using consolidative samarium with docetaxel after docetaxel plus estramustine induction yielded promising survival and durable pain relief,[28] but no definitive data exist regarding the combination. A randomized phase III trial of docetaxel alone or with strontium or with zoledronic acid (the TRAPEZE trial) found no delay in SREs or pain progression, and no impact on survival although the combination was well tolerated.[29] The development of additional radiopharmaceutical agents has been a goal in order to optimize safety and efficacy and facilitate further combination and consolidation studies.

Radium-223

Radium-223 is an alpha-emitting calcium mimetic, designed with the intention of decreasing collateral damage to the marrow seen with beta-emitting particles, which can safely be administered repeatedly in hopes of greater antineoplastic efficacy. The Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer (ALSYMPCA) trial randomized 928 men with pain (of any intensity) related to bone metastases from mCRPC, who had either progressed on docetaxel, declined docetaxel, or were not docetaxel candidates, to receive radium-223 50 kBq kg^{-1} IV over 1 min each month ×6 or placebo IV each month ×6 in conjunction with standard care.[28] Standard of care at that time included ketoconazole, androgen receptor antagonists, estrogens, and glucocorticoids, and bisphosphonate therapy was permitted. Men with known visceral metastases were excluded, but malignant lymphadenopathy <3 cm in short-axis diameter was allowed. Adequate hematologic function is required. Before the first administration of radium-223, the absolute neutrophil count (ANC) was required to be $\geq 1.5 \times 10^9$ l^{-1}, the platelet count $\geq 100 \times 10^9$ l^{-1}, and hemoglobin ≥10 g dl^{-1}. Before subsequent administrations of radium-223, the ANC was required to be $\geq 1 \times 10^9$ l^{-1} and the platelet count $\geq 50 \times 10^9$ l^{-1}. The primary end point was overall survival and the main secondary end point was time to symptomatic skeletal-related event (sSRE). Most patients (58%) had received docetaxel. A significant increase in overall survival was observed, with median survival of 14.9 months for patients treated with radium-223 and 11.3 months for the placebo group (HR: 0.7, 95% CI: 0.58–0.83; $P < 0.001$). Notably, the benefit was observed in the context of 41% of patients receiving concurrent bisphosphonate therapy, although patients did not receive denosumab; questions remain regarding optimal timing and relative contribution of antiresorptive agents during treatment with radium-223. Data from the key trials finding clinical benefit from bone-targeted therapy are summarized in **Table 1**.

Optimal dosing of radium-223 is the subject of further investigation. Earlier in development, doses of 25 kBq kg^{-1}, 50 kBq kg^{-1}, and 80 kBq kg^{-1} every 6 weeks were evaluated. PSA responses (>50% decline) were noted in 13% of patients treated with the 80 kBq dose compared to 6% with 50 kBq and 0 for 25 kBq; a similar trend was noted for 30% PSA decline. Pain relief was highest in the 50 kBq dose cohort, but SREs were similar across cohorts. This raises questions of optimal dosing, and the results of a randomized phase III study comparing the standard 50 kBq kg^{-1} every 4 weeks for 6 doses to experimental arms of 80 kBq kg^{-1} every 4 weeks for 6 doses or 50 kBq kg^{-1} every 4 weeks for 12 doses are eagerly anticipated (NCT02023697). Additional important steps will be required to delineate optimal sequencing and combination strategies for this agent. Selected ongoing and completed randomized studies with radium-223 are summarized in **Table 2**. A preliminary study of radium-223 in combination with docetaxel found tolerability for the combination (not done as consolidation, as with the samarium/strontium studies, but rather administered together from the start), and compared to docetaxel alone, progression-free survival was improved (12 months compared to 9.3 months).[30]

There are also phase II trials combining radium-223 with immune checkpoint inhibitors such as atezolizumab and pembrolizumab.

FITTING BONE-TARGETED THERAPY INTO THE EVOLVING LANDSCAPE FOR mCRPC

Improved cancer control with androgen pathway agents including abiraterone and enzalutamide has been associated with reduction in SREs. With abiraterone in mCRPC, there was a delay in median time to first SRE from 20.3 months to 25.0 months (HR: 0.615, 95% CI: 0.478–0.791).[29] For enzalutamide in mCRPC, a delay in median time to first SRE from 13.3 months to 16.7 months (HR: 0.69, 95% CI: 14.6–19.1) was noted.[30] In these trials, 42% and 43% of patients were taking bisphosphonates, respectively. The value of bisphosphonate and RANK-ligand therapy in the context of the improved osseous control in the era of abiraterone and enzalutamide will need to be re-assessed. For now, patients should receive bone supportive therapy in addition to life-extending therapy in the castration-resistant setting. Similarly, the contribution of bisphosphonates and RANK-ligand inhibitors during radium-223 treatment remains to be clarified. As agents traditionally used in the CRPC setting move up into frontline therapy for metastatic prostate cancer based on trials such as ChemoHormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED), LATITUDE, and STAMPEDE, questions related to the marginal value of bone-targeted therapy and optimal utilization will become even more important.

CONCLUSIONS

Reducing skeletal-related morbidity remains a key goal of palliative life-extending therapy in metastatic prostate cancer. New data about dosing schedules and combinations of these agents will continue to refine the optimal strategy for incorporating bone-targeted therapy into treatment paradigms for prostate cancer.

Table 1: Summary of key trials supporting the use of bone-targeted agents in prostate cancer treatment

Agent	*Dosing schedule*	*Indication*	*Study*	*Outcome measures*
ZA	4 mg IV q3–4 weeks	mCRPC	Saad *et al*. 2002[19]	11% reduction in SRE compared to placebo
Denosumab	120 mg SQ q month, 60 mg SQ q6 months	mCRPC; any, with ADT	Fizazi *et al*. 2011[29]; Smith *et al*. 2012[30]	HR=0.82, reduction in SRE versus ZA; HR=0.38, reduction in vertebral fractures
Radium-223	50 kBq kg^{-1} IV q month × 6 doses	mCRPC; symptomatic bone metastasis	Parker *et al*. 2013[48]	HR=0.7, overall survival versus placebo; HR=0.66, time to symptomatic SRE

ADT: androgen deprivation therapy; IV: intravenously; HR: hazard ratio; mCRPC: metastatic castration-resistant prostate cancer; q: every; SQ: subcutaneously; SRE: skeletal-related event; ZA: zoledronic acid

Table 2: Selected ongoing or completed studies of radium-223 in combination with or sequenced with androgen-targeted and other systemic therapies for advanced prostate cancer

Trial	*Arms*	*Disease state*	*Accrual goal*
NCT02463799	Sipuleucel-T Sip-T + radium-223	mCRPC, prior abiraterone/enzalutamide OK	34
NCT02034552	Radium-223; radium-223 + abiraterone; radium-223 + enzalutamide	mCRPC, prior docetaxel OK	64
NCT02043678	Abiraterone + radium-223; abiraterone + placebo	mCRPC, no prior treatment	806
NCT02194842	Enzalutamide + radium-223; enzalutamide	mCRPC, no prior treatment except up-front docetaxel	560
NCT03230734	Radium-223; docetaxel	mCRPC, any prior treatment, no LN >3 cm short axis	70
NCT02814669	Radium-223; atezolizumab	mCRPC, prior abiraterone/enzalutamide no visceral metastases	45
NCT03093428	Radium-223; pembrolizumab	mCRPC, any prior therapy no visceral metastases	45

mCRPC: metastatic castration-resistant prostate cancer; LN: lymph node.

AUTHOR CONTRIBUTIONS

TBD and NA contributed to the conception, writing, and editing. TBD also performed literature search. Both authors read and approved the final manuscript.

COMPETING INTERESTS

TBD is the consultant for Bayer, Janssen, and formerly speaker for Astellas. NA is the consultant for Pfizer, Novartis, Merck, Genentech, Eisai, Exelixis, Clovis, and EMD Serono.

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