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Collaborative Review – Prostate Cancer

New and Emerging Therapies for Bone Metastases in Genitourinary Cancers

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Abstract

Context: Bone metastases are a common feature of advanced genitourinary malignancies and a prominent cause of morbidity and mortality.
Objective: The objective of this review is to discuss the incidence, pathophysiology, and management of bone metastases in the most prevalent genitourinary malignancies.
Evidence acquisition: We reviewed the relevant medical literature, with a particular emphasis on prospective randomized controlled trials. Much of the relevant clinical trial data focus on prostate cancer (PCa). We provide a nonsystematic review and our perspective on the available data.
Evidence synthesis: Clinical manifestations can include pain, hypercalcemia, pathologic fractures, and spinal cord compression. Optimal systemic therapy for skeletal metastases often features a combination of disease-specific therapy and bone-targeted therapy. Some agents, such as the radiopharmaceutical radium-223, blur the line between those categories. Osteoclast inhibition is a validated strategy in the management of selected patients with bone metastases. Zoledronic acid, a bisphosphonate, is approved for the prevention of skeletal events caused by solid tumors metastatic to bone. Denosumab is a fully human monoclonal antibody that inactivates receptor activator of nuclear factor-κB ligand and is approved for the same indication. Beta-emitting radiopharmaceuticals can be effective for the palliation of pain caused by bone metastases, but their use is often limited by marrow suppression. The alpha-emitting radiopharmaceutical radium-223 has recently been shown to improve overall survival and prevent skeletal events in select men with castration-resistant PCa metastatic to bone. Multiple ongoing clinical trials are designed to examine the potential for therapeutic inhibition of additional targets such as Src and hepatocyte growth factor (MET).
Conclusions: Bone metastases cause considerable morbidity and mortality among patients with genitourinary malignancies. Optimal management requires consideration of bone-targeted therapy as well as disease-specific therapy. Further research is needed to optimize the use of existing agents and to define the therapeutic potential of novel targets.

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1. Introduction

Prostate, kidney, and bladder and urothelial cancers are the most common genitourinary malignancies. The natural history of each can feature bone metastases. This review describes the prevalence, pathophysiology, and management of bone metastases resulting from these cancers.

Prostate cancer (PCa) is the second leading cause of cancer death in men (see Table 1). Bone metastases are by far the most prominent metastatic site, particularly within the axial skeleton [1]. PCa bone metastases generally appear dense or blastic on plain films but cause structural compromise and greatly elevate the risk for fractures. They are often detectable by technetium-99m methylene diphosphonate (^{99}mTc-MDP) bone scan, an established component of disease assessment in PCa clinical trials [2]. Without bone-targeted therapy, the rate of skeletal-related events (SREs; ie, pathologic fracture, spinal cord compression, surgery to bone, or radiation to bone) in men with castration-resistant PCa (CRPC) metastatic to bone in one trial was approximately 44% (fracture rate of 22%) at 15 mo [3,4].

Kidney cancer is the sixth to ninth most common cancer, depending on the region. Bone is second only to lung as a prevalent site of metastases [5]. In patients with metastatic disease, the incidence of bone metastases is approximately 30% [5–7]. These metastases are often but not always detectable by bone scan. Without bone-targeted therapy, the rate of SREs in patients with renal cell carcinoma (RCC) metastatic to bone in one trial was 74% at 1 yr [8,9].

Bladder cancer (BCa) is the fourth to sixth most common cancer, depending on the region. Among patients with metastatic disease, the incidence of bone metastases is approximately 30% [10]. The rate of SREs in patients with urothelial cancer metastatic to bone is >50% at 1 yr [11].

2. Evidence analysis

We reviewed the relevant medical literature, with a particular emphasis on prospective randomized controlled trials. PubMed search terms included *prostate cancer, transitional cell carcinoma, renal cell carcinoma, bone metastases, osteoclast*, and *skeletal related events*. We provide a focused, nonsystematic review and our perspective on the available data.

3. Evidence synthesis

3.1. Normal and pathologic bone physiology

Skeletal integrity is maintained by a balance between new bone formation by osteoblasts and bone resorption by osteoclasts. Osteoblasts synthesize and secrete organic matrix that is then mineralized to form new bone. Osteoclasts bind bone and create an acidified resorption vacuole into which they secrete bone-resorbing enzymes [12]. Resultant breakdown of bone matrix liberates numerous factors that can in turn stimulate osteoblast activity (eg, transforming growth factor-β, insulin-like growth factors I and II, fibroblast growth factors, platelet-derived growth factors) [13].

Osteoclast regulation is complex but prominently features receptor activator of nuclear factor-κB (RANK) signaling [12]. RANK is a cell surface receptor present on osteoclasts throughout much of their life cycle. RANK ligand (RANKL) binding to RANK promotes differentiation of osteoclast precursors. It is also important to activation and survival of mature osteoclasts. Major sources of RANKL within the bone microenvironment include stromal cells, osteoblasts, and activated T-cells [14–16].

Bone metastases are clearly associated with an increase in bone turnover. Two widely studied bone turnover markers are urinary N-telopeptide (uNTx) and bone-specific alkaline phosphatase (BAP): uNTx reflects collagen breakdown by osteoclasts, and BAP is the bone-specific isoform of alkaline phosphatase (AP) and is elevated in the presence of bone formation by osteoblasts. Correlation is strong between total serum AP and BAP levels [17].

Osteoclasts contribute greatly to the pathophysiology of bone metastases caused by solid tumors. Osteoclast-mediated bone resorption can weaken the structural integrity of bone and can liberate growth factors that may stimulate osteoblasts and tumor cells. Markers of elevated osteoclast activity are associated with adverse clinical outcomes [18–22]. Osteoclast inhibition is therefore a rational therapeutic strategy. Two classes of osteoclast-targeted drugs are approved for this indication. Radiopharmaceuticals represent a third class of approved bone-targeted therapy. Multiple additional classes of agents are in clinical development.

Table 1 – Incidence, mortality, and skeletal complications resulting from genitourinary cancers in Europe and the United States

	Europe [66]		United States [67]		Approximate incidence of SREs* when metastatic to bone
	New cases, no.	Deaths, no.	New cases, no.	Deaths, no.	
Prostate	382 300	89 300	241 740	28 170	CRPC: 44% for SRE; 22% for fracture [3,4]
Kidney	88 400 (36.6% women)	39 300 (36.9% women)	64 770 (37.8% women)	13 570 (36.2% women)	74% for SRE; 40% for fracture [5,8,9]
Bladder	139 500 (21.4% women)	51 300 (24.6% women)	73 510 (24.4% women)	14 880 (29.4% women)	>50% for SRE [11]
Testicular	18 300	1700	8590	360	Poorly described

SRE = skeletal-related event; CRPC = castration-resistant prostate cancer.
SREs: pathologic fracture, spinal cord compression, surgery to bone, or radiation to bone.

3.2. Classes of available bone-targeted therapies

3.2.1. Bisphosphonates

Bisphosphonates are a class of chemically simple organic pyrophosphate analogs that inhibit osteoclast function. The agents are taken up by osteoblasts and deposited within areas of active bone remodeling. Once incorporated within bone, they likely exert long-lasting effects on osteoclasts that encounter them.

3.2.2. Receptor activator of nuclear factor-κB ligand inhibitors

RANK is a central regulator of differentiation, activation, and survival of osteoclasts. Denosumab is a fully human monoclonal antibody that binds avidly and specifically to RANKL, inactivating it. Bioavailability is high with subcutaneous administration. Dosing varies by indication. It has been used at 60 mg every 6 mo for the management of osteoporosis and at 120 mg every 4 wk for the management of bone metastases. Dosing is not affected by renal insufficiency.

3.3. Toxicities of osteoclast-targeted therapies

There are a number of potential toxicities of potent osteoclast inhibition (see Table 2). Hypocalcemia is common but is frequently asymptomatic and without clinical consequence. Completed trials have generally recommended or required daily supplemental oral calcium (≥500 mg) and vitamin D (≥400 IU) [3,23]. Flu-like acute-phase reaction can occur in the wake of intravenous (IV) bisphosphonates but is generally self-limited. Osteonecrosis of the jaw (ONJ) is relatively uncommon but can have substantial negative clinical impact on patients who experience it. Nephrotoxicity has been observed with zoledronic acid but can generally be avoided with appropriate dosing, infusion time, and patient selection. Although RANKL plays a role in immune function through the regulation of interactions between T-cells and dendritic cells [15,24,25], infection rates appear to be unaffected [23,26–29].

3.3.1. Radiopharmaceuticals

Radiopharmaceuticals are systemically administered bone precursors that emit radiation or are linked to a radioactive emitter, enabling the delivery of radiation preferentially to areas of high bone turnover. Beta-emitting radiopharmaceuticals strontium-89, Samarium-153-ethylene diamine tetramethylene phosphonate (^{153}Sm-EDTMP), and rhenium-186 hydroxyethyledine diphosphonate (Re-186 HEDP) can palliate pain caused by bone metastases and are approved for this purpose [30]. One frequent dose-limiting toxicity is marrow suppression caused by beta particle penetration to adjacent marrow. Radium-223 is a newer alpha-emitting agent not yet approved. Alpha-particle penetration (≤100 μm) is far less than that of beta particles (several millimeters), making cytopenias less common [31]. In addition, alpha particles are larger than beta particles and produce high linear energy transfer radiation that may lead to more DNA double-strand breaks.

3.4. Clinical trial end points

Clinical trials that study bone-targeted therapies generally feature end points that include time to first bone metastasis, SREs, bone turnover markers, and overall survival (OS). SREs are a composite end point that is typically defined as any of

Table 2 – Notable toxicities of osteoclast-targeted therapies*

Toxicity	Approximate incidence	Management/notes
Hypocalcemia	Zoledronic acid: approximately 6% (1% grade 3–4) Denosumab: approximately 11–13% (2–5% grade 3–4), higher if impaired renal function	Many cases are asymptomatic. Severe or symptomatic cases can lead to hospitalization for calcium repletion. We recommend serum 25-OH vitamin D testing and repletion prior to initiation. We recommend oral calcium (500–1000 mg daily) and vitamin D3 (600–1000 IU daily).
Acute-phase reaction	Zoledronic acid: approximately 15–18% Denosumab: approximately 7–8%	Characterized by flu-like symptoms such as malaise, myalgias, and fever. Generally occurs within 24 h of dosing and resolves without specific intervention.
Osteonecrosis of the jaw (ONJ)	1–2% with zoledronic acid or denosumab in phase 3 trials of metastatic solid tumors [23,28,29] 4–5% over 3–4 yr with monthly denosumab for metastasis prevention [40]	Exposed nonhealing bone of the jaw [68,69]. Key risk factors include drug potency, duration of therapy, and invasive dental procedures [70,71]. Published guidelines focus on maintenance of good oral hygiene and avoidance of invasive dental procedures during therapy [72–76].
Nephrotoxicity	Zoledronic acid: nephrotoxicity was notably observed in the 039 phase 3 study with 8-mg dose and 5-min infusion time [3]; nephrotoxicity is rare with current practice Denosumab: not observed	Acute tubular necrosis [77]; severity ranges from mild/reversible to irreversible and requiring hemodialysis. Zoledronic acid package insert recommends 15-min infusion time, 4-mg maximum dose, and specific dose modifications for stable renal dysfunction with creatinine clearance >30 ml/min [78].

CRPC = castration-resistant prostate cancer.

* Unless otherwise noted, incidence and grade are listed for monthly use of either zoledronic acid (4 mg) or denosumab (120 mg). Estimates are taken from phase 3 studies involving men with CRPC metastatic to bone [23] and a mixed population of patients with solid tumors or multiple myeloma involving bone [29].

the following: pathologic fracture, spinal cord compression, surgery to bone, or radiation to bone. Osteoclast-targeted therapies such as zoledronic acid and denosumab have gained regulatory approval on the basis of their abilities to prevent or delay SREs.

Some studies, therefore, have used a standardized definition of SREs as a regulatory end point for osteoclast-targeted therapies. Other studies have examined some version of SREs as an exploratory end point. When used in this context, SRE has often been defined differently. New hormonal agents such as abiraterone acetate and enzalutamide (MDV3100) have demonstrated reductions in SREs [32,33], providing evidence that control of tumor growth can reduce the risk of bone complications. The incidence of SREs was not an end point in the phase 3 trials of several disease-modifying systemic therapies that improved OS (eg, docetaxel, sipuleucel-T, cabazitaxel); therapeutic impact on SREs by those agents is therefore difficult to discern.

Many trials examine and report the effect of bone-targeted therapy on OS. Completed trials of the most potent available osteoclast inhibitors have shown that this strategy does not affect OS [4,23]. In contrast, the radiopharmaceutical radium-223 demonstrated an ability to both prevent SREs [34] and improve OS [31]. It is common for trials of bone-targeted agents to formally examine bone turnover markers such as uNTx and BAP, as discussed later.

3.5. Osteoclast inhibition for castration-resistant prostate cancer metastatic to bone

Among men with PCa, the population at highest risk for SREs is those with CRPC metastatic to bone. Several trials have examined osteoclast inhibition in this setting. The comparatively weak bisphosphonates clodronate and pamidronate did not significantly reduce the incidence of SREs. Zoledronic acid and denosumab have each been shown to produce benefit and are approved for this indication. See Table 3 for a summary of notable trials of osteoclast inhibition for PCa.

Zoledronic acid was the first drug to reduce SREs in this clinical setting in the 039 trial [3,4]. That study enrolled 643 men with CRPC and bone metastases. Participants were randomized to treatment every 3 wk with zoledronic acid (4 mg or 8 mg) or placebo. The trial was positive. as SREs occurred in a greater proportion of those who received placebo (33.2% with zoledronic acid 4 mg vs 44.2% with placebo; 95% confidence interval [CI], −20.3 to −1.8; $p = 0.021$). Median time to first SRE was also significantly longer with zoledronic acid 4 mg (488 d with zoledronic acid vs 321 d with placebo; $p = 0.009$) [31]. There were no significant differences in end points such as disease progression, OS, performance status (PS), or quality of life (QoL). Compared to placebo, mean increase in pain score at 15 mo was significantly less with zoledronic acid 8 or 4 mg but not significantly less with zoledronic acid 4 mg.

The zoledronic acid 039 trial was also notable for nephrotoxicity with zoledronic acid. This observation led to two midtrial changes. The 8-mg treatment arm was dose-reduced to 4 mg, and the infusion time was lengthened from 5 min to 15 min. These changes have shaped subsequent use of the drug on and off of trials.

Denosumab was later compared directly to zoledronic acid and shown to be superior in the 103 phase 3 trial [23]. That trial enrolled 1904 men with metastatic CRPC. They were randomized to denosumab (120 mg subcutaneously) or zoledronic acid (4 mg IV) every 4 wk. The trial was positive, as denosumab lengthened time to first on-study SRE (20.7 mo vs 17.1 mo; hazard ratio [HR]: 0.82; 95% CI, 0.71–0.95; $p = 0.0002$ for noninferiority; $p = 0.008$ for superiority; see Fig. 1). ONJ was observed in 1–2% of the study cohort (12 cases with zoledronic acid, 22 cases with denosumab; $p = 0.09$). OS did not differ. Pain was not formally evaluated.

Zoledronic acid and denosumab have each been shown to reduce the incidence of SREs in men with CRPC metastatic to bone and are approved in this setting. We recommend use of one of the two agents in men with CRPC metastatic to bone who do not have contraindications to therapy. In this setting, the optimal timing for starting treatment has not been directly addressed in clinical trials. It is reasonable to consider therapy in patients at high risk for SREs (eg, those with multiple bony lesions, those with lesions at risk because of their anatomic location, or those with a previous history of SREs).

National Comprehensive Cancer Network guidelines state that "choice of agent may depend on underlying comorbidities, whether the patient has been treated with zoledronic acid previously, logistics, and/or cost considerations." Which factors most compellingly cause clinicians to choose one over the other? Availability and cost are important factors that are beyond the scope of this review. Three factors favor denosumab in certain settings. First, denosumab produced superior time to first SRE (20.7 mo vs 17.1 mo; HR: 0.82; 95% CI, 0.71–0.95; $p = 0.008$ for superiority) [23]. This is a modest but significant advantage. Second, zoledronic acid is not recommended for patients with a glomerular filtration rate (GFR) <30. Denosumab has not been formally studied in patients with GFR <30 but is a reasonable option in this population. Third, a subcutaneous injection is usually more convenient than an IV injection.

3.6. Osteoclast inhibition with first-line androgen-deprivation therapy for prostate cancer

Osteoclast inhibition in combination with first-line androgen-deprivation therapy (ADT) for metastatic PCa is not an established strategy for preventing skeletal events. Clodronate failed to demonstrate a clinical benefit in this setting [35,36]. Zoledronic acid has not shown a benefit in this setting but is under study for men with hormone-sensitive bone metastases from PCa in two ongoing phase 3 trials designed to evaluate SREs (NCT00242567 and NCT00079001). One of those—the CALGB/CTSU 90202 trial—was prematurely closed to new accrual in April 2012 because of lack of sufficient study drug. Although

Table 3 – Notable completed clinical trials of osteoclast inhibition in advanced prostate cancer

Study	No.	Population	Study arms	End points	Outcome/notes
National Cancer Institute of Canada Clinical Trials Group Pr06 [79]	209	CRPC with symptomatic bone metastases	All received mitoxantrone (12 mg/m^2 every 3 wk) 1:1 randomization to clodronate (1500 mg IV) or placebo every 3 wk	Primary: palliative response as assessed by present pain intensity index Secondary: symptomatic PFS, OS, QoL	No significant difference in palliative response (46% with clodronate vs 39% with placebo; $p = 0.54$) or in secondary end points such as symptomatic PFS, OS, and QoL.
CGP 032 and INT-05 (combined analysis) [80]	378	CRPC with symptomatic bone metastases	1:1 randomization to pamidronate (90 mg IV) or placebo every 3 wk for 27 wk	Self-reported pain score, analgesic use, incidence of SREs, mobility	No significant difference in pain, analgesic use, or SREs. Urinary bone resorption markers such as uNTx were significantly suppressed with therapy.
Trial 039 [3,4]	643	CRPC with bone metastases	1:1:1 randomization to zoledronic acid (4 mg or 8 mg) or placebo every 3 wk	Proportion of patients with SREs, time to first SRE, skeletal morbidity rate, pain and analgesic scores, and disease progression	Significant decrease in SREs (33.2% with zoledronic acid 4 mg vs 44.2% with placebo), trend toward improved survival. Zoledronic acid 8 mg was modified because of nephrotoxicity.
Trial 103 [23]	1904	CRPC with bone metastases	1:1 randomization to denosumab (120 mg s.c.) versus zoledronic acid (4 mg IV) every 4 wk	Primary: time to first on-study SRE and was assessed for noninferiority Secondary: superiority in time to first SRE, OS	Denosumab lengthened time to first on-study SRE (20.7 mo vs 17.1 mo; HR: 0.82; 95% CI, 0.71–0.95; $p = 0.0002$ for noninferiority; $p = 0.008$ for superiority).
Medical Research Council Pr05 [35,36]	311	PCa with bone metastases, starting or responding to first-line ADT	1:1 randomization to oral clodronate (2.080 mg) versus placebo daily; maximum 3 yr of treatment	Primary: symptomatic bone progression–free survival Secondary: OS, PS	Nonsignificant trend toward improved bone progression–free survival (HR: 0.70; 95% CI, 0.61–1.02; $p = 0.066$). Long-term follow-up revealed an improvement in OS with clodronate treatment (HR: 0.77; 95% CI, 0.60–0.98; $p = 0.032$) [35], currently regarded as hypothesis generating.
Medical Research Council Pr04 [35,37]	508	Nonmetastatic PCa, within 3 yr of diagnosis	1:1 randomization to oral clodronate (2.080 mg) versus placebo daily for up to 5 yr	Symptomatic bone metastasis–free survival	There was no improvement in symptomatic bone metastasis–free survival (HR: 1.22; 95% CI, 0.88–1.68) or survival (HR: 1.02; 95% CI, 0.80–1.30).
Trial 704 [38]	201 (closed early)	Nonmetastatic CRPC	1:1 randomization to zoledronic acid (4 mg IV) or placebo every 4 wk	Bone metastasis–free survival	Halted early for futility because of lower-than-expected rate of bone metastases. With placebo, median bone metastasis–free survival was 30 mo; PSA >10 ng/ml and PSA DT were significantly associated with risk.
Trial 147 [40]	1432	Nonmetastatic CRPC with PSA ≥8 μg/l or PSA DT ≤10.0 mo	1:1 randomization to denosumab (120 mg s.c.) or placebo every 4 wk	Bone metastasis–free survival	Denosumab increased bone metastasis–free survival by 4.2 mo (median: 29.5 mo with denosumab vs 25.2 mo with placebo; HR: 0.85; 95% CI, 0.73–0.98; $p = 0.028$). It is not approved for this indication.

CRPC = castration-resistant prostate cancer; IV = intravenous; PFS = progression-free survival; OS = overall survival; QoL = quality of life; SRE = skeletal-related event; uNTx = urinary N-telopeptide; s.c. = subcutaneous; HR = hazard ratio; CI = confidence interval; PCa = prostate cancer; ADT = androgen-deprivation therapy; PS = performance status; PSA = prostate-specific antigen; DT = doubling time.

follow-up is ongoing, this early closure may compromise the ability to detect a clinically important difference between early and standard use of zoledronic acid.

Regulatory approvals for denosumab and zoledronic acid are broader than that supported by level 1 evidence. They are European Medicines Agency (EMA) and US Food and Drug Administration (FDA) approved for patients with solid tumors metastatic to bone. Osteoclast inhibition has never been shown to produce benefits in men with PCa who have not yet developed castration resistance. Metastatic hormone-naïve PCa is unique in that it is so frequently responsive to first-line disease-modifying therapy. Further, the relatively long natural history would lead to a duration of therapy every 4 wk, which far exceeds those durations that have been studied in trials. This would likely lead to an increase in treatment-related morbidity, particularly ONJ. We argue against the use of either agent prior to the development of CRPC.

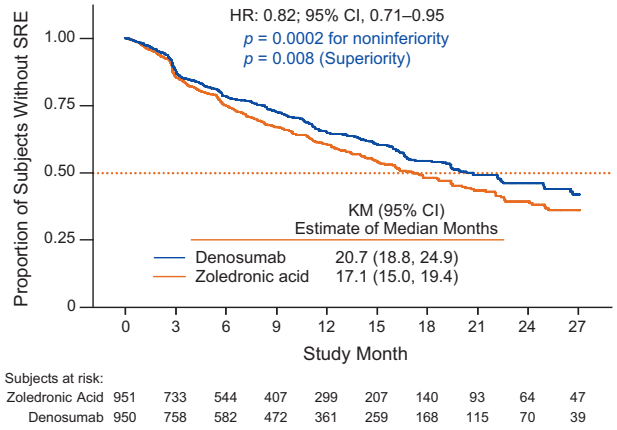

Fig. 1 – Kaplan-Meier estimates of time to first on-study skeletal-related event for men with castration-resistant prostate cancer metastatic to bone. Subjects were assessed from baseline to the primary analysis cut-off date.
CI = confidence interval; HR = hazard ratio.
*** *p* values were adjusted for multiplicity [23]. Reprinted with permission. Copyright 2011. All rights reserved.**

It is important to note that osteoclast inhibition for the prevention of treatment-related osteoporotic fractures is an important topic but is beyond the scope of this review. Treatment regimens for this indication differ substantially from those designed to prevent skeletal events caused by bone metastases.

3.7. *Osteoclast inhibition for prostate cancer metastasis prevention*

Osteoclast inhibition for the prevention of bone metastases is not an approved strategy. Clodronate [35,37] and zoledronic acid [38] have thus far failed to demonstrate benefits in this setting. Denosumab was the first agent to produce a statistically significant delay in the initial onset of bone metastases but was not approved for this indication.

Zoledronic acid is under ongoing study in the Zometa European Study (ZEUS) [39] and STAMPEDE (NCT00268476) trials. The ZEUS trial has enrolled 1433 men with nonmetastatic CRPC and at least one of the following high-risk factors: prostate-specific antigen (PSA) ≥20 ng/ml, lymph node–positive disease, or Gleason score ≥8 cancer. They are randomized one to zoledronic acid or placebo every 3 mo for 48 mo. The primary end point is the proportion of men with at least one bone metastasis. STAMPEDE is a seven-arm phase 2/3 trial that plans to enroll 4000 men with high-risk localized, metastatic, or relapsed PCa. It examines several combinations of ADT, zoledronic acid, docetaxel, abiraterone, and celecoxib. The primary outcome is OS.

In the 147 trial, denosumab was the first agent to demonstrate a statistically significant delay in time to first bone metastasis [40]. That study enrolled 1432 men with nonmetastatic CRPC and at least one of the following factors associated with risk for bone metastases: PSA ≥8.0 μg/l or PSA doubling time (DT) ≤10.0 mo. Participants were randomized to denosumab (120 mg subcutaneously) or placebo every 4 wk. The trial was positive, as denosumab increased bone metastasis–free survival by 4.2 mo (29.5 mo vs 25.2 mo; HR: 0.85; 95% CI, 0.73–0.98; $p = 0.028$). Symptomatic bone metastases were significantly less common with denosumab (69 cases vs 96 cases; HR: 0.67; 95% CI, 0.49–0.92; $p = 0.01$) but were relatively uncommon. OS did not differ. Exploratory analysis indicated a larger effect on bone metastasis–free survival among men with a PSA DT ≤6 mo [41].

The FDA Oncology Drug Advisory Committee recommended against approval for metastasis prevention. The briefing document cited the lack of impact on survival, pain, and health-related QoL. It also cited the 5% incidence of ONJ in the treatment group.

3.8. *Clinical use of bone turnover markers*

The role of bone turnover markers such as uNTx and total and bone AP in clinical practice is presently not well defined. Marker levels are clearly prognostic, as they correlate with meaningful clinical outcomes such as SREs, cancer progression, and survival [18–22,42–44]. They have been widely used in clinical trials as evidence of on-target effects in bone, but their use outside of trials is more limited. Professional guidelines are largely silent on their clinical use. Turnover markers are not clearly predictive, as no systemic therapy has been convincingly shown to be more or less effective based on marker levels, although recent data preliminarily suggest greater benefit with radium-223 among patients with high baseline BAP levels [31]. We argue that prognostic information alone does not justify the widespread use of these markers in clinical practice. In specific circumstances, however, they may rationally guide the escalation of osteoclast-targeted therapy.

3.8.1. *Escalation*

Suboptimal marker suppression could be taken as a cue to escalate therapeutic intensity. As neither zoledronic acid nor denosumab has been studied at a dose more often than every 3–4 wk, shortening the dosing interval cannot be safely pursued outside of a trial. Neither agent has been extensively studied at above-typical doses (denosumab 120 mg or zoledronic acid 4 mg) or in combination with the other. Change of agent is presently the only available strategy for escalating intensity.

Denosumab appears to be the more potent inhibitor of osteoclast function. It is superior in suppressing bone turnover markers [23,28,29,45], superior at preventing SREs resulting from breast cancer [28] or CRPC [23], and produces higher rates of hypocalcemia [23,28,29]. In patients receiving zoledronic acid, therefore, a switch to denosumab represents an escalation in therapeutic intensity. It is rational to consider such a switch in the presence of persistently elevated uNTx levels (eg, >50 nmol/l bone collagen equivalents/mM) despite ongoing zoledronic acid. In the phase 3 039 trial in metastatic CRPC, approximately 20% of the participants receiving zoledronic acid had uNTx

levels above this threshold [17]. This strategy has been the subject of phase 2 study [45,46]. We argue that this is a reasonable clinical use of uNTx. However, given the limited evidence that a switching strategy results in clinical benefit, this strategy should be tested prospectively.

3.8.2. De-escalation

Marker suppression beyond the 4-wk dosing interval of either agent may provide a rationale for less frequent dosing. The safety of holding treatment until markers rise would need to be established in a large clinical trial designed to demonstrate noninferiority in the incidence of SREs. The Bisphosphonate Marker (BISMARK) trial is an example of this. It will randomize 1500 women with metastatic breast cancer to receive either typical zoledronic acid dosing or potentially less-frequent dosing as guided by uNTx levels. That trial is in follow-up. Given the absence of mature clinical trial data, this strategy cannot yet be recommended.

3.9. Radiopharmaceuticals for prostate cancer

Systemically administered radiopharmaceuticals first demonstrated efficacy in the palliation of pain caused by bone metastases from prostate and other cancers. Several beta-emitting radiopharmaceuticals (strontium-89, ^{153}Sm-EDTMP, and Re-186 HEDP) are approved for this indication [30]. Strontium-89 has also been tested to consolidate chemotherapy in CRPC and shown to improve OS in a phase 2 trial [47]. The most prominent limitation of these agents is myelosuppression.

Some studies have suggested a potential for the combination of radiopharmaceuticals with other systemic therapies [47,48]. Combination therapy is under study in two notable phase 3 trials. A US National Cancer Institute–sponsored study combines strontium-89 with either docetaxel with prednisone or the ketoconazole, adriamycin, vinblastine, estramustine regimen (NCT00024167). The UK TRAPEZE trial (NCT00554918) randomizes men with CRPC metastatic to bone to receive one of four regimens: (1) docetaxel with prednisolone; (2) docetaxel, prednisolone, and zoledronic acid; (3) docetaxel, prednisolone, and strontium-89; or (4) docetaxel, prednisolone, zoledronic acid, and strontium-89.

Given the palliative efficacy of beta emitters and the theoretical advantages of alpha-emitting agents, the phase 3 ALSYMPCA trial was designed to study the effect of radium-223 on OS. That study enrolled 922 men with symptomatic CRPC, at least two bone metastases, and no visceral metastases. Just over half (58%) of the patients had received prior docetaxel treatment. They were randomized 2:1 to receive six monthly treatments with radium-223 (50 kBq/kg IV) or placebo. The trial was positive, as median OS was significantly longer with radium-223 (14.9 mo vs 11.3 mo; HR: 0.695; 95% CI, 0.581–0.832; $p = 0.00007$) [49]. Radium also improved time to first SRE (15.6 mo vs 9.8 mo; HR: 0.658; 95% CI, 0.522–0.830; $p = 0.00037$) [34]. Myelosuppression was slightly more common with treatment than with placebo (grades 3 and 4 neutropenia: 2.2% vs 0.7%; grades 3 and 4 thrombocytopenia 6.3% vs 2%). Regulatory review of the radium-223 data is ongoing but will likely result in approval of this agent for men with CRPC and symptomatic bone metastases.

One interesting subgroup analysis of the ALSYMPCA trial found that men with high baseline BAP levels experienced greater relative benefit [31]. Another found that men who received concomitant zoledronic acid with radium-223 experienced greater relative benefit. This may be related to the dual inhibition of bone turnover or to the reduced bone turnover and prolonged dwell time for radium in bone when given with osteoclast inhibition. Further study of radium-223 with other, concomitant bone-targeted and disease-specific therapies is needed to clarify these effects.

It is important to note that external-beam radiation therapy can provide effective and tolerable palliation of pain caused by individual metastatic lesions or regions. A large majority of patients experience some pain relief with this strategy [50]. Although some anatomic locations necessitate fractionation, many studies have made effective use of single-fraction therapy [51].

3.10. Src inhibition for prostate cancer

Src inhibition is a rational potential strategy for the management of bone involvement by cancer, particularly PCa. Src is one within a family of nonreceptor protein tyrosine kinases that are responsible for a diverse range of signal transduction pathways downstream of cell-surface receptors (eg, GFRs and cytokine receptors). Src is thought to be involved in both the pathogenesis of PCa bone metastases and the regulation of osteoclast function [52,53].

Dasatinib is a potent oral inhibitor of Src family kinases and other kinases and is a prominent agent within this class [54,55]. The combination of dasatinib and docetaxel demonstrated promising safety and activity in a phase 2 study [56] and became the subject of the phase 3 READY trial (NCT00744497). That study completed accrual and was designed to enroll 1500 men with chemotherapy-naïve metastatic CRPC and randomize them to docetaxel and prednisone with or without dasatinib 100 mg daily. The primary end point is survival.

3.11. Hepatocyte growth factor inhibition for prostate cancer

Hepatocyte growth factor (MET) has emerged recently as a potentially important target. Cabozantinib (XL184) is an orally administered tyrosine kinase inhibitor that prominently inhibits vascular endothelial growth factor receptor (VEGFR)-2 (IC50 0.035 nmol/l) and MET (IC50 1.3 nmol/l) [57]. In early-phase study, it dramatically improved ^{99}mTc-MDP bone scan evidence of disease in a high percentage of men with CRPC metastatic to bone [58,59]. This degree of treatment-induced improvements on bone scans has not previously been observed with VEGF-targeted agents [60,61] or with other MET inhibitors. The clinical significance, durability, and mechanisms

responsible for these bone scan responses have not been well defined.

On the strength of this preliminary activity, cabozantinib is the subject of two phase 3 trials among men with PCa. Each will enroll men with CRPC metastatic to bone and progressive despite docetaxel and either abiraterone or enzalutamide (MDV3100). COMET 1 (NCT01605227) does not require cancer-related pain. Men will be randomized to cabozantinib or prednisone. The primary end point is OS. COMET 2 (NCT01522443) requires pain caused by bone metastases. Men will be randomized to cabozantinib or mitoxantrone with prednisone. The primary outcome measure is confirmed pain response at week 12 durable since week 6.

Rolotumumab (AMG-102) is a fully human MET-neutralizing antibody [62] that did not produced significant benefits in a randomized phase 2 study [63].

3.12. Renal cell and urothelial cancers of bladder and upper tract

Many clinical trials of bone-targeted therapies in advanced solid tumors focus on the most common diseases: PCa and breast cancer. Patterns of drug development outside of breast and prostate cancers have favored single trials with mixed populations or analyses of subsets of patients included in larger phase 3 trials. Nonetheless, clinicians must make rational use of this lower level of evidence.

Zoledronic acid produced benefits in a placebo-controlled phase 3 trial that enrolled a heterogeneous population of patients with nonbreast, nonprostate cancers involving bone [64]. Compared to placebo, zoledronic acid was associated with lower rates of at least one SRE at 21 mo (39% vs 46%) and longer median time to first SRE (236 d vs 155 d; $p = 0.009$).

Denosumab and zoledronic acid demonstrated similar efficacy in a more recent phase 3 trial that enrolled patients with nonbreast, nonprostate cancers involving bone [29]. Denosumab was noninferior to zoledronic acid in median time to first SRE (HR: 0.84; 95% CI, 0.71–0.98; $p = 0.0007$; Fig. 2). RCC and urothelial cancers composed subsets within each of these two pivotal trials.

3.12.1. Renal cell carcinoma

Management of RCC metastatic to bone can reasonably be guided by the zoledronic acid and denosumab trials described earlier. In particular, retrospective subset analysis of patients with RCC enrolled in the placebo-controlled zoledronic acid trial ($n = 74$) revealed that zoledronic acid significantly reduced the proportion of patients with an SRE (37% vs 74% with placebo; $p = 0.015$; Fig. 3) [9]. Either of the two agents is reasonable in this clinical setting.

Patients with bone-metastatic RCC have one of the highest rates of SREs of any solid tumor [65]. In the placebo-controlled zoledronic acid trial, the 9-mo incidence of an SRE in the placebo arm was 74% with RCC compared to 44% for the overall trial population [9,64]. A reduction in skeletal events is therefore likely to have a greater clinical impact in this group. The reduction in SRE incidence with zoledronic acid was associated with improvements in progression rates, and the relative improvement was particularly high in RCC [8]. Thus, zoledronic acid is a reasonable choice for preventing SREs in patients with bone-metastatic RCC if renal function is adequate.

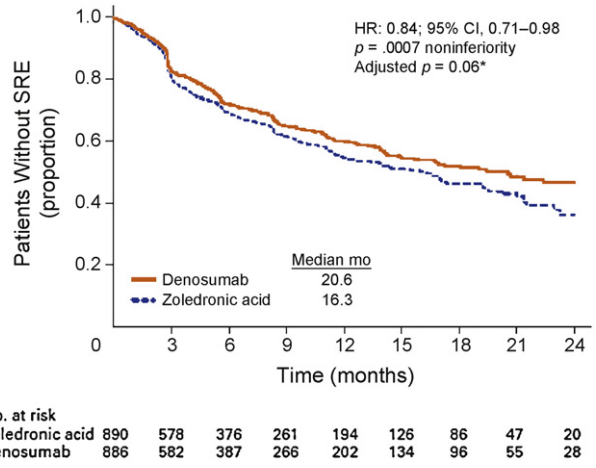

Fig. 2 – Kaplan-Meier estimate of time to first on-study skeletal-related events for subjects with multiple myeloma or nonbreast, nonprostate solid tumors metastatic to bone.
SRE = skeletal-related event; HR = hazard ratio; CI = confidence interval.
*** Adjusted for multiplicity [29]. Reprinted with permission. Copyright 2010 American Society of Clinical Oncology. All rights reserved.**

3.12.2. Bladder cancer

Bladder and upper tract urothelial cancers metastatic to bone are also managed as directed by the pivotal phase 3 trials of zoledronic acid and denosumab. Urothelial cancers are seldom the subject of dedicated phase 3 study using bone-targeted agents. Zoledronic acid did demonstrate benefits in one small randomized prospective trial ($n = 40$) [11]. That study enrolled patients with bone metastases from BCa who were receiving palliative radiation therapy. They were randomized to zoledronic acid or placebo monthly for 6 mo. The primary end point was positive, as zoledronic acid produced a lower proportion of patients who had developed ≥1 SRE at 12-mo follow-up (60% vs 90%

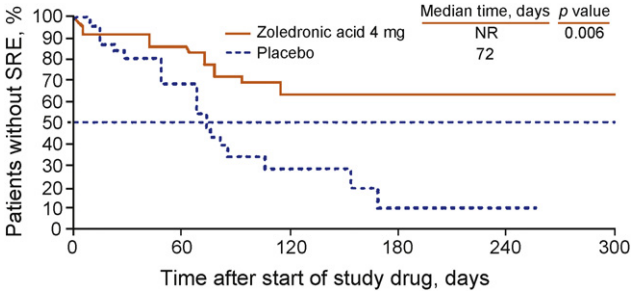

Fig. 3 – Kaplan-Meier estimates of time to first skeletal-related event in patients with bone metastases from renal cell carcinoma during a 9-mo trial of zoledronic acid. Data presented are for those who received 4 mg zoledronic acid ($n = 27$) or placebo ($n = 19$).
SRE = skeletal-related event; NR = not reached.
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Table 4 – Evidence-based use of osteoclast inhibition for genitourinary cancers

Clinical setting	Evidence-based use	Notes
PCa metastatic to bone and responding to first-line ADT	No osteoclast inhibition	Two ongoing phase 3 trials are expected to clarify the potential role of zoledronic acid in this clinical setting.
CRPC that is not metastatic to bone	No osteoclast inhibition	Denosumab prolonged bone metastasis–free survival in selected patients in this setting but is not approved for this clinical indication for a variety of reasons.
CRPC metastatic to bone	In the absence of contraindications, either of the following two options: - Denosumab 120 mg every 4 wk - Zoledronic acid every 4 wk	Denosumab is modestly but significantly superior for this indication. Appropriate dental care prior to initiation of therapy is important. Daily calcium (≥500 mg) and vitamin D (≥400 IU) supplementation are recommended. GFR <30 ml/min is a contraindication for zoledronic acid and requires additional attention to calcium/phosphate monitoring when using denosumab.
Renal cell or bladder/urothelial carcinoma metastatic to bone	In the absence of contraindications, either of the following two options: - Denosumab 120 mg every 4 wk - Zoledronic acid every 4 wk	Efficacy of the two drugs was similar in head-to-head study within a heterogeneous population of patients with metastatic solid tumors (nonbreast, nonprostate). RCC metastatic to bone carries a particularly high risk for SREs, making this a strong indication for osteoclast inhibition.

PCa = prostate cancer; ADT = androgen-deprivation therapy; CRPC = castration-resistant prostate cancer; GFR = glomerular filtration rate; RCC = renal cell carcinoma; SRE = skeletal-related event.

with placebo; $p = 0.010$). Secondary end points such as median time to first SRE and 1-yr OS were also significantly improved.

3.12.3. *Regulatory approvals*

Zoledronic acid and denosumab have each gained FDA and EMA approval for the prevention of SREs from solid tumors metastatic to bone. Author recommendations are summarized in Table 4.

4. Conclusions

Bone metastases cause substantial clinical burden among patients with genitourinary malignancies. Management of patients with bone metastases is often best accomplished with a combination of disease-specific therapy and bone-targeted therapy. Research is needed to define optimal use of available therapies and therapeutic potential for new targets.

Author contributions: Philip J. Saylor had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Saylor and Pienta.
Acquisition of data: Saylor.
Analysis and interpretation of data: Saylor.
Drafting of the manuscript: Saylor.
Critical revision of the manuscript for important intellectual content: Armstrong, Fizazi, Freedland, Saad, Smith, Tombal, Pienta, Saylor.
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