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The role of bisphosphonates or denosumab in light of the availability of new therapies for prostate cancer

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ABSTRACT

Most men with advanced prostate cancer will develop bone metastases, which have a substantial impact on quality of life. Bone metastases can lead to skeletal-related events (SREs), which place a burden on patients and healthcare systems. For men with castration-resistant prostate cancer (CRPC) and bone metastases, the treatment landscape has evolved rapidly over the past few years. The relatively recent approvals of the hormonal agents abiraterone acetate and enzalutamide, second-line chemotherapy cabazitaxel, and the radiopharmaceutical radium-223 dichloride (radium-223), have provided clinicians with a greater choice of treatments. These compounds have benefits in terms of overall survival based on the results of pivotal phase 3 studies. The bisphosphonate zoledronic acid and the RANK ligand inhibitor denosumab are indicated for the prevention of SREs in men with metastatic CRPC but studies of these compounds have not demonstrated a survival benefit. The important question of the role of bisphosphonates or denosumab in combination with these new agents has thus materialised. Current and emerging evidence from clinical studies of abiraterone acetate, enzalutamide and radium-223, suggest that addition of bisphosphonates or denosumab to these new therapies may provide further clinical benefits for patients with prostate cancer and bone metastases. This evidence may help to shape clinical practice but are based largely on *post hoc* analyses of clinical trial data. It is therefore apparent that further data are required from both clinical studies and real-world settings to enable physicians to understand the efficacy and safety of combination therapy with the new agents plus bisphosphonates or denosumab.

Introduction

Since the approval of docetaxel in 2005 by the European Medicines Agency (EMA) [1], the number of treatments extending the overall survival (OS) of patients with metastatic castration-resistant prostate cancer (mCRPC) has increased substantially. These treatments include the chemotherapy cabazitaxel, the hormone therapies abiraterone acetate (AA) and enzalutamide, and the radiopharmaceutical radium-223 dichloride (radium-223) [2–5].

Prostate cancer preferentially metastasises to bone, with skeletal metastases being present in up to 90% of patients with metastatic disease [6]. Metastatic bone disease appears early in the course of the disease, so a substantial proportion of patients with cancer will develop bone pain. Bone metastases also reduce the quality of life of patients [7], Skeletal complications may occur and can require radiotherapy and/or surgery. Skeletal complications are frequently aggregated into a single clinical endpoint, skeletal-related events (SREs; pathologic fracture, radiation or surgery to bone, and spinal cord compression). On average, patients with bone metastatic mCRPC experience a SRE every 3–6 months during their last year of life [8], placing a considerable burden on the patients themselves and on healthcare systems. In addition, in patients with prostate cancer, the adjusted 1-year mortality was 4.7-fold higher in those with bone metastases alone, and 6.6-fold higher in those with bone metastases and SREs, compared with individuals with no metastases or SREs [9]. SREs may be indicative of more advanced or aggressive disease, thus leading to increased mortality. The term SREs includes asymptomatic fractures that are radiologically detected but which have an unclear clinical relevance [10]; thus, some trials have used symptomatic-skeletal events (SSE) as a term and composite endpoint when only referring to symptomatic events (SSEs are defined as radiation to bone, symptomatic pathologic fracture, surgery to bone or symptomatic spinal cord compression) [8].

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Inhibitors of bone resorption, such as the receptor activator of nuclear factor kappa B ligand (RANKL) inhibitor denosumab and the bisphosphonate zoledronic acid (ZA), are approved for the prevention of SREs in adults with advanced malignancies involving bone, including prostate cancer [11,12].

There is some evidence that administering ZA in combination with chemotherapy is beneficial in patients with mCRPC. In the phase 3 TRAPEZE (Taxotere® RadioisotoPE ZomEta®) study, the addition of ZA to docetaxel therapy was found to have a beneficial effect on skeletal morbidity compared with docetaxel alone, even though there was no benefit in terms of OS [13]. However, there is now emerging evidence from *post hoc* analyses of data from pivotal phase 3 studies that combination therapy comprising bisphosphonates or denosumab plus AA or enzalutamide or radium-223 may increase survival, as well as conferring additional benefit in terms of preventing skeletal complications in men with mCRPC [14–16]. Given the potential impact of SREs on patients' health, it is important to consider the role of new therapies alongside bisphosphonates or denosumab to gain a better understanding of the potential involvement of combination therapy.

Pathophysiology of bone metastases in prostate cancer

Bone remodelling is a normal, dynamic process that is characterised by osteoclast-mediated bone resorption followed by osteoblast-induced bone formation. The process is closely regulated by a range of factors including hormones, cytokines and growth factors [17–19].

Bone metastases can disrupt the bone remodelling process, leading to a cycle of bone destruction [20,21]. The bone marrow microenvironment may act as a reservoir for malignant cells and, once they are within the bone microenvironment, prostate tumour cells have the capacity to produce a wide range of cytokines and growth factors that stimulate cells of osteoblastic lineage [21,22]. These, in turn, activate osteoclasts, leading to increased bone resorption. Activated osteoclasts can then release growth factors from the bone matrix that further stimulate tumour growth and activity [20,21,23]. The increased osteoclast activity is not confined to metastatic sites, and can be more generalised [19].

Patients with metastatic prostate cancer commonly experience SREs owing to increased osteolysis in typically osteoblastic bone lesions [19,24]. On imaging, bone metastases in prostate cancer typically appear to be osteoblastic in nature, but there is thought to be a role for osteoclasts too, with bone resorption thought to precede bone formation [19,20]. In preclinical models of prostate cancer, osteoclast inhibition prevents bone metastases [25,26]. Osteoclast activation therefore plays a significant role in the development of metastases.

In addition, androgen deprivation therapy (ADT) can lead to cancer treatment-induced bone loss (CTIBL), which increases bone resorption, impairs bone stability and increases the risk of fractures in early-stage prostate cancer, and can also increase the risk of SREs in patients with metastatic prostate cancer [27,28].

Bisphosphonates or denosumab in men with castration-resistant prostate cancer and bone metastases

Until recently, ZA and the RANKL inhibitor denosumab, which are both indicated to prevent SREs in patients with advanced solid tumours (Table 1) [11,12] were the only licensed agents available to reduce the incidence of SREs in patients with prostate cancer. Table 2 summarises the pivotal phase 3 studies of both the compounds and the new therapies [11,12,29–42]. In a placebo-controlled study of 643 men with mCRPC, fewer patients had at least one SRE following treatment with intravenous ZA 4 mg every 3 weeks versus placebo (38% vs 49% at 24 months, $p = 0.028$) [31]. ZA reduced the overall risk of skeletal complications by 36% at 24 months [31], and bone pain increased less compared with placebo [29]. In a phase 3, placebo-controlled, double-blind study of 1904 men with mCRPC, treatment every 4 weeks with

Table 1
Summary of key characteristics and EU indications for denosumab, zoledronic acid, enzalutamide, abiraterone acetate and radium-223 [3–5,11,12].

	Abiraterone acetate	Enzalutamide	Radium-223	Zoledronic acid	Denosumab
Agent class	Hormone therapy that inhibits 17α-hydroxylase/C17,20-lyase (CYP17)	Hormone therapy that inhibits the androgen receptor	α-particle emitter	Bisphosphonate	Human monoclonal antibody against RANK ligand
Dosing frequency	1000 mg orally once daily with prednisone or prednisolone 10 mg once daily	160 mg orally once daily	55 kBq/kg IV every 4 weeks	4 mg IV every 3–4 weeks	120 mg SC every 4 weeks
Half-life	15 h	5.8 days	11.4 days	6 days	28 days
EU approval year	2011	2013	2013	2001	2011
Indication	mCRPC in men who are asymptomatic, or mildly symptomatic, after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated or in those whose disease has progressed on or after a docetaxel-based chemotherapy regimen	mCRPC in men who are asymptomatic, or mildly symptomatic, after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated, or in those whose disease has progressed on or after a docetaxel-based chemotherapy regimen	men with CRPC, symptomatic bone metastases and no known visceral metastases	Prevention of SREs in adults with advanced malignancies involving bone	Prevention of SREs in adults with bone metastases from solid tumours

CRPC, castration-resistant prostate cancer; EU, European Union; IV, intravenous; mCRPC, metastatic CRPC; radium-223; radium-223 dichloride; SC, subcutaneous; SRE, skeletal-related event.

Table 2
Summary of pivotal phase 3 studies of denosumab, zoledronic acid, enzalutamide, abiraterone acetate and radium-223, showing study characteristics and key endpoints/outcomes [14,16,29–42].

Study	Drug	Control	Profile	Primary endpoint	Secondary endpoints	Safety
Abiraterone acetate						
COU-AA-302 [14,36]	Abiraterone (1000 mg/day) plus prednisone (5 mg b.d.)	Prednisone (5 mg b.d.) plus placebo	Phase 3, chemotherapy-naïve mCRPC; N = 1088	OS: 34.7 vs 30.3 months; HR: 0.81 ($p = 0.0033$)	Time to decline in ECOG PS score: 12.3 vs 10.9 months ($p = 0.005$); time to initiation of cytotoxic chemotherapy: 25.2 vs 16.8 months ($p < 0.001$); time to opiate use: 33.4 vs 23.4 months ($p < 0.0001$)	AEs ≥ grade 3: 54% vs 44%
COU-AA-301[35,38]	Abiraterone (1000 mg/day) plus prednisone (5 mg b.d.)	Prednisone (5 mg b.d.) plus placebo	Phase 3, mCRPC (previous docetaxel); N = 1195 (2:1 ratio)	OS[a]: 15.8 vs 11.2 months; HR: 0.74 ($p < 0.0001$)	TTP[b] (PSA): 8.5 vs 6.6 months ($p < 0.001$); PFS[b]: 5.6 vs 3.6 months ($p < 0.001$); PSA response[b]: 29% vs 5.5% ($p < 0.0001$); time to first SRE[c]: 25.0 vs 20.3 months ($p = 0.0001$)	AEs ≥ grade 3 in > 5% of patients in the abiraterone arm[b]: fatigue (9.1% vs 10.4%); anaemia (7.8% vs 8.1%); back pain (7.1% vs 10.2%); bone pain (6.4% vs 7.6%); arthralgia (5% vs 4%)
Enzalutamide						
AFFIRM[40,41]	Enzalutamide (160 mg/day)	Placebo	Phase 3; CRPC (previous docetaxel); N = 1199	OS: 18.4 vs 13.6 months; HR: 0.63 ($p < 0.001$)	Proportion of patients with ≥ 50% reduction in PSA level: 54% vs 2% ($p < 0.001$); soft-tissue response rate: 29% vs 4% ($p < 0.001$); quality of life response rate: 43% vs 18% ($p < 0.001$); time to PSA progression: 8.3 vs 3.0 months ($p < 0.001$); radiographic PFS: 8.3 vs 2.9 months ($p < 0.001$); time to first SRE: 16.7 vs 13.3 months ($p < 0.001$)	Grade ≥ 3 AEs in > 5% of patients in the enzalutamide arm: fatigue (6% vs 7%)
PREVAIL[39,42]	Enzalutamide(160 mg/day)	Placebo	Phase 3; chemotherapy-naïve CRPC; N = 1717	Radiographic OS at 12 months: 65% vs 14%; HR: 0.19($p < 0.001$) OS: 32.4 vs 30.2 months; HR: 0.71($p < 0.001$)	Time to chemotherapy initiation: 28.0 vs 10.8 months ($p < 0.001$); time to first SRE: 31.1 vs 31.3 months ($p < 0.001$); time to PSA progression: 11.2 vs 2.8 months ($p < 0.001$)	Grade ≥ 3 AEs: 43% vs 37%
Radium-223						
ALSYMPCA[6,16]	Radium-223(50 kBq/kg qw for six injections)	Placebo	Phase 3; CRPC with bone metastases; N = 921 (2:1)	OS: 14.9 vs 11.3 months; HR: 0.70($p < 0.001$)	Overall time to SRE: 15.6 vs 9.8 months ($p < 0.0037$) time to SRE (sensitivity analysis): 14.7 vs 8.1 months ($p < 0.0001$); time to increase in ALP level: 7.4 vs 3.8 months ($p < 0.00001$): time to increase in PSA level: 3.6 vs 3.4 months ($p < 0.00001$)	Grade ≥ 3 AEs in > 5% of patients in the radium-223 arm: anaemia (13% vs 13%), thrombocytopenia (7% vs 2%); bone pain (21% vs 26%)
Zoledronic acid						
Saad et al.[29] Saad et al. [31]	Zoledronic acid (4 mg q3w or 8 mg → 4 mg q3w)	Placebo	Phase 3; mCRPC; N = 643	SRE at 15 months (zoledronic acid 4 mg vs zoledronic acid 8/4 mg vs placebo): 33.2% vs 38.5% vs 44.2% ($p = 0.021$ for zoledronic acid 4 mg vs placebo); SRE at 24 months: 38% vs 41% vs 49% ($p = 0.028$ for zoledronic acid 4 mg vs placebo)	Time to first SRE at 24 months: 488 vs 363 vs 321 days; HR (zoledronic acid 4 mg vs placebo): 0.68 ($p = 0.009$). At 15 months uNTx reduced by ~ 70% with zoledronic acid ($p = 0.001$); pain scores increased more with placebo	At 15 months, renal function deterioration during infusion (15.2% vs 20.7% vs 11.5%); grade 3 creatinine increase (3.3% vs 2.3% vs 1.0%); myalgia (24.8% vs 24.3% vs 17.8%); fever (20.1% vs 22.0% vs 13.0%)

(*continued on next page*)

Table 2 (*continued*)

Study	Drug	Control	Profile	Primary endpoint	Secondary endpoints	Safety
Denosumab						
Fizazi et al.[30] Smith et al.[34] von Moos et al.[32]	Denosumab (120 mg q4w) plus placebo	Zoledronic acid (4 mg q4w) plus placebo	Phase 3; bisphosphonate-naïve mCRPC; N = 1904 Integrated analysis of three phase 3 studies in solid tumours; N = 5544	Time to first SRE: 20.7 vs 17.1 months; HR: 0.82 ($p = 0.0002$, non-inferiority; $p = 0.008$, superiority)	Time to first and subsequent SREs: rate ratio 0.82 ($p = 0.008$); uNTx reduction: 84% vs 69% ($p < 0.0001$); OS: 19.4 vs 19.8 months; TTP: 8.4 vs 8.4 months; risk of developing first SSE: HR 0.78 ($p = 0.005$); time to first and subsequent SSEs: rate ratio 0.78 ($p = 0.004$); risk of developing moderate-to-severe pain during the study for patients with a first on-study occurrence of a SSE: HR 3.07, 95% CI 2.34–4.03 ($p < 0.0001$); or of a SRE: HR 2.09, 95% CI 1.69–2.58 ($p < 0.0001$) In integrated analysis of three phase 3 studies in solid tumours: median time until moderate-to-severe pain: median 6.5 vs 4.7 months, HR, 0.83 ($p < 0.001$); relative difference of patients progressing from no strong opioid use (AQA score 0–2) to strong opioid use (AQA score ≥ 3): –13.4% ($p = 0.041$)	Grade 3/4 AEs: 72% vs 66% ($p = 0.01$); hypocalcaemia: (13% vs 6%; $p < 0.0001$); ONJ (1.8% vs 1.3%; $p < 0.09$); acute phase reactions (8% vs 18%); per protocol dose adjustments for renal impairment (0% vs 22%); per protocol doses withheld owing to renal impairment (0% vs 15%)

Unless otherwise specified, all comparisons indicated refer to drug versus control groups. If there is no p value given for a comparison the difference in values is not statistically significant.
AE, adverse event; ALP, alkaline phosphatase; ALSYMPCA, ALpharadin in SYMPtomatic prostate CAncer patients; AQA, Analgesic Quantification Algorithm; b.d., twice daily; CRPC, castration-resistant prostate cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; mCRPC, metastatic castration-resistant prostate cancer; NR, not reached; ONJ, osteonecrosis of the jaw; ORR, objective response rate as per modified response evaluation criteria in solid tumours; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen; q, every; SRE, skeletal-related event; SSE, symptomatic skeletal event; TTP, time to progression; uNTx, urinary N-telopeptide; w, weeks.

[a] Final analysis.

[b] Interim analysis.

[c] Exploratory analysis.

subcutaneous denosumab 120 mg was shown to be superior to intravenous ZA 4 mg every 4 weeks for the time to first SRE, and to first and subsequent SREs [30]. The time to first SRE was extended from 17.1 to 20.7 months (hazard ratio [HR]: 0.82; 95% CI: 0.71–0.95; $p = 0.008$ for superiority). Denosumab significantly reduced the risk of first and subsequent SREs by 18% compared with ZA (rate ratio: 0.82; 95% CI: 0.75–0.89; $p = 0.001$ for superiority) [30]. Denosumab also had a greater benefit in terms of slowing pain progression compared with ZA. In patients with no-to-mild pain at baseline, denosumab significantly increased the time until development of moderate-to-severe pain compared with ZA (median: 6.5 vs 4.7 months; HR: 0.83; $p < 0.001$; 17% risk reduction), and fewer patients receiving denosumab compared with ZA progressed to the use of strong opioids (Table 2) [32]. OS (HR: 1.03; 95% CI: 0.91–1.17; $p = 0.65$) and investigator-reported disease progression (HR: 1.06; 95% CI: 0.95–1.18; $p = 0.30$) were similar in the two treatment groups [30]. The beneficial effect on SREs of denosumab relative to ZA was found regardless of baseline characteristics, such as Eastern Cooperative Oncology Group performance status (ECOG PS), number of bone metastases, presence or absence of visceral metastases or urinary N-telopeptide level (a commonly used marker of bone turnover) [33]. A *post hoc* analysis of the integrated study results has also shown that, compared with ZA, denosumab reduced the frequency and significantly reduced the risk of SSEs ($p < 0.005$; Table 2). Overall, similar beneficial effects of treatment on bone pain were observed for SREs and SSEs (Table 2) [34].

New therapies combined with bisphosphonates or denosumab and their effects on bone health in men with castration-resistant prostate cancer and bone metastases.

New therapies have changed the face of mCRPC treatment, improving survival and pain control, and having a positive effect on the bone health of patients [6,35,36,41,42].

Abiraterone acetate

Oral AA 1000 mg once daily was approved in the EU in 2011 (Table 1). It is indicated with prednisone or prednisolone 10 mg once daily for the treatment of mCRPC in men who are asymptomatic, or mildly symptomatic, after failure of ADT in whom chemotherapy is not yet clinically indicated, or in those whose disease has progressed on or after a docetaxel-based chemotherapy regimen [5]. Two pivotal, placebo-controlled studies investigated AA plus prednisone (Table 2) [35,36].

The concomitant use of bisphosphonates or denosumab was investigated in a *post hoc* analysis of the placebo-controlled COU-AA-302 study and provides clinical evidence regarding a possible beneficial additive effect of these agents with AA in men with mCRPC [14]. In COU-AA-302, AA plus prednisone therapy significantly increased the median OS compared with prednisone alone in a cohort of 1088 chemotherapy-naïve men with mCRPC who were asymptomatic or mildly symptomatic (Table 2) [36]. Benefits of AA were also observed for pain palliation but the effects on SRE occurrence were not investigated [36,37]. A total of 353 patients (34% [184/546] of the AA group, 31% [169/542] of the prednisone group) were receiving concomitant bisphosphonates or denosumab. Of these 353 patients, 93% were treated with ZA, 6% with denosumab and the remaining 1% with other bisphosphonates. A total of 336 (95%) individuals were receiving bisphosphonates or denosumab at baseline and another 17 (5%) commenced therapy with these agents during the study [14]. The baseline characteristics of patients receiving or not receiving concomitant bisphosphonates/denosumab were broadly similar across treatment groups, except that a greater proportion of patients using bisphosphonates/denosumab had a Gleason score ≥ 8 (57% vs 50%), bone disease (93% vs 76%), and bone metastasis (55% vs 39%). Concomitant use of bisphosphonates or denosumab was found to improve OS (Fig. 1)

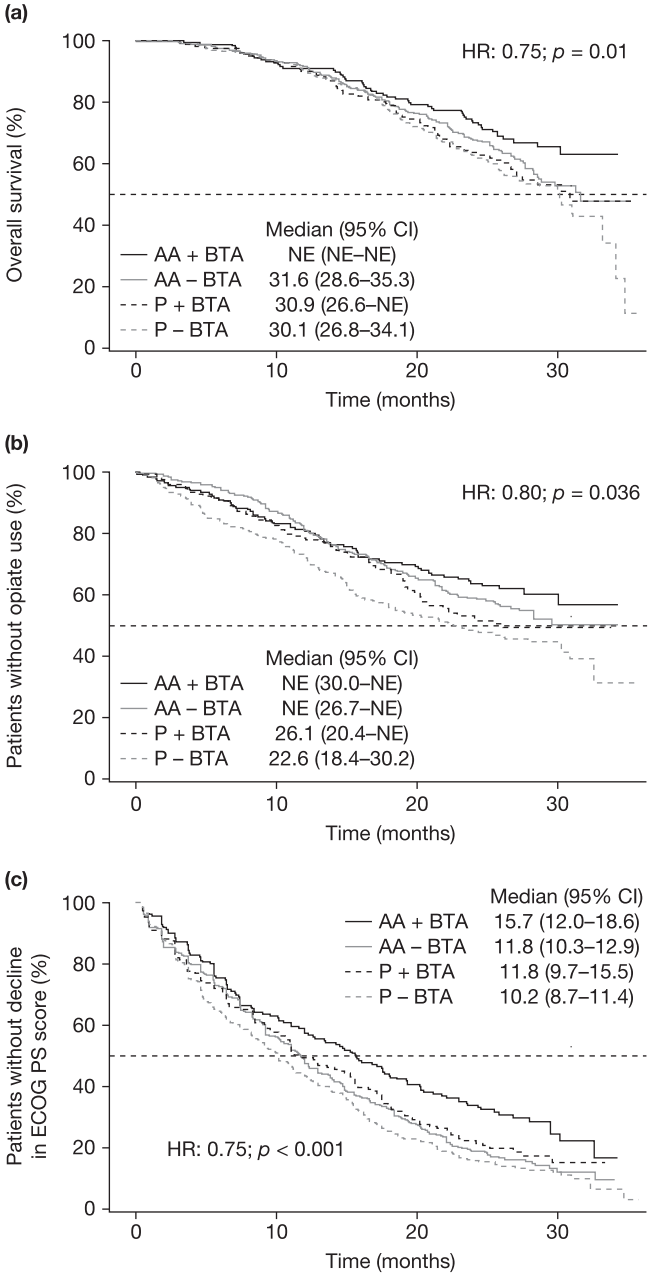

Fig. 1. Kaplan–Meier plots of (a) overall survival, (b) time to opiate use for cancer-related pain and (c) time to deterioration in ECOG PS score by ≥1 point for AA and concomitant bisphosphonates or denosumab use. Reproduced (with permission) from Saad et al. [14]. AA, abiraterone acetate; BTA, bone-targeted agent; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; NE, not estimable; P, prednisone.

compared with no use of these agents (HR: 0.75; 95% CI: 0.60–0.94; $p = 0.012$), based on a median follow-up of 27.1 months. A longer time to deterioration in ECOG PS (HR: 0.75; 95% CI: 0.64–0.87; $p < 0.001$) and longer time to opiate use for cancer-related pain (HR: 0.80; 95% CI: 0.65–0.99; $p = 0.036$) were also seen with concomitant use of bisphosphonates or denosumab compared with no use of these agents (Fig. 1) [14].

Enzalutamide

Oral enzalutamide 160 mg once daily was approved in the EU in 2013 (Table 1) [3]. Like AA, enzalutamide is indicated for the treatment of mCRPC in men who are asymptomatic, or mildly symptomatic, after

failure of ADT in whom chemotherapy is not yet clinically indicated, or in those whose disease has progressed on or after a docetaxel-based chemotherapy regimen [3].

Two pivotal, placebo-controlled, phase 3 studies investigated enzalutamide in men with mCRPC, providing interesting findings regarding the effect of baseline bisphosphonate or denosumab use [41,42]. The PREVAIL study of 1717 chemotherapy-naïve men with mCRPC examined the effect of enzalutamide versus placebo on OS and radiographic progression-free survival (rPFS) as the co-primary endpoints [42]. At baseline, approximately 17% of patients in both groups had more than 20 bone metastases, and 26% of patients in the enzalutamide group and 27% in the placebo group were receiving bisphosphonates or denosumab [43]. Beneficial effects on both OS and rPFS were observed with enzalutamide, with a 29% reduction in the risk of death compared with placebo (HR: 0.71; 95% CI: 0.60–0.84; $p < 0.001$)[42]. Enzalutamide also reduced the median time to first SRE (HR: 0.72; 95% CI: 0.61–0.84; $p < 0.0001$) and had benefits in terms of pain progression compared with placebo [39].

Of note, the results of subgroup analyses indicated that enzalutamide provided numerically greater benefit in terms of rPFS than placebo for patients who were *not* receiving bisphosphonates or denosumab at baseline (HR: 0.16; 95% CI: 0.12–0.21) compared with those who were (HR: 0.27; 95% CI: 0.18–0.41) (Fig. 2) [42]. However, it is of note that the study was not designed or powered to test these interactions nor analysed the effect on SREs for this subgroup. It is possible that confounding factors (such as patient age and disease severity) should be considered before concluding that concomitant bisphosphonates or denosumab may have a negative effect on SREs when patients are treated with enzalutamide. Therefore, it may be useful to physicians if a similar *post hoc* analysis, adjusted for confounding factors, was conducted in order to examine the effect of baseline concomitant use of bisphosphonates or denosumab on the time to development of SREs in patients receiving enzalutamide, in addition to the effect on rPFS or OS. Additional *post hoc* analyses of the PREVAIL study have indicated that the benefit of enzalutamide on rPFS and OS could be greater for patients with a low volume of bone disease (defined in this analysis as < 4 bone metastases at screening) who may be less likely to receive bisphosphonates or denosumab at this earlier disease stage, versus a high volume of bone disease (≥4 bone metastases at screening) [43]. However, the differences between these groups in OS and rPFS were not formally statistically tested and so should be interpreted with caution [43].

In the AFFIRM study of 1199 men with mCRPC previously treated with docetaxel, enzalutamide had a beneficial effect on OS, with a 37% reduction in the risk of death compared with placebo (HR: 0.63; 95% CI: 0.53–0.75; $p < 0.001$) (Fig. 2) [41]. At baseline, 43% of patients in both groups were receiving bisphosphonates, and 38% had more than 20 bone metastases [40,41]. In a *post hoc* analysis, beneficial effects of enzalutamide were also observed on SREs, health-related quality of life and pain palliation [40]. The median time to first SRE in the enzalutamide group was 16.7 months compared with 13.3 months in the placebo group (HR: 0.69: 95% CI: 0.57–0.84; $p = 0.0001$). This effect was seen irrespective of bisphosphonate or corticosteroid use at baseline [40].

Radium-223

Radium-223 was approved in the EU in 2013 (Table 1) and is indicated for the treatment of men with mCRPC, symptomatic bone metastases and no known visceral metastases [4]. The dose regimen of radium-223 is an activity of 55 kBq per kg body weight, given at 4-week intervals for six injections [4].

The effect of radium-223 on OS was investigated in the pivotal phase 3, placebo-controlled ALpharadin in SYMPtomatic prostate CAncer patients (ALSYMPCA) study of 921 men with CRPC and bone metastases [6]. Patients were stratified at baseline based on ineligibility or refusal to receive docetaxel chemotherapy. At baseline, approximately 40% of the patients were receiving bisphosphonates and approximately 30% had more than 20 bone metastases [6]. Treatment with radium-223 led to a survival benefit compared with placebo (median: 14.9 months vs 11.3 months; HR: 0.70; 95% CI: 0.58–0.83; $p < 0.001$) [6]. Radium-223 significantly prolonged the time to an increase in the total alkaline phosphatase (ALP) level (HR: 0.17; 95% CI: 0.13–0.22; $p < 0.001$) [6], delayed the need for external-beam radiation therapy [44] and improved patient health-related quality of life versus placebo [45]. In a *post hoc* sensitivity analysis, the time to first SSE was significantly longer with radium-223 (median 14.7 months) than with placebo (8.1 months; HR: 0.63; 95% CI: 0.50–0.79; $p < 0.0001$) [16].

The results of *post hoc* analyses from the ALSYMPCA study indicate that bisphosphonates have a beneficial additive effect on bone health when given in combination with radium-223 [16]. A greater benefit of radium-223 over placebo on the time to first SSE was observed in patients who received bisphosphonates at baseline (HR: 0.49; 95% CI: 0.33–0.74; $p = 0.00048$) compared with those who did not (HR: 0.77; 95% CI: 0.58–1.02; $p = 0.07$) (Fig. 3) [16]. Baseline use of bisphosphonates was associated with a decreased risk of SSEs in a multivariate analysis (HR: 0.49; 95% CI: 0.38–0.64; $p < 0.001$) [16].

Findings from a prospective, phase 3b, early access programme of radium-223 in 696 men with mCRPC have indicated that, in patients receiving concomitant treatment with denosumab, there is a greater beneficial effect on OS than in those not receiving concomitant denosumab (Fig. 4) [46]. At baseline, 60% of patients had received previous chemotherapy with docetaxel. Of those receiving concomitant therapy, 20% were treated with denosumab, 19% with bisphosphonates, 20% with AA and 5% with enzalutamide [46]. In radium-223-treated patients, OS was longer in those treated concomitantly with denosumab (median OS in months: NA [not available]; 95% CI: 15–NE [not estimable]) than in those who did not receive denosumab (median OS in months: 13; 95% CI: 12–NE) [46]. In this study, benefits in terms of OS with radium-223 treatment were observed in patients with a good ECOG PS, no pain and low ALP levels [46]. The concomitant use of AA or enzalutamide with radium-223 also had beneficial effects on OS in this study; no effect of concomitant bisphosphonate use on OS was observed [46].

Considerations for combination therapy for men with castration-resistant prostate cancer and bone metastases

When considering a combination of therapies for men with CRPC and bone metastases, the compounds selected should have differing

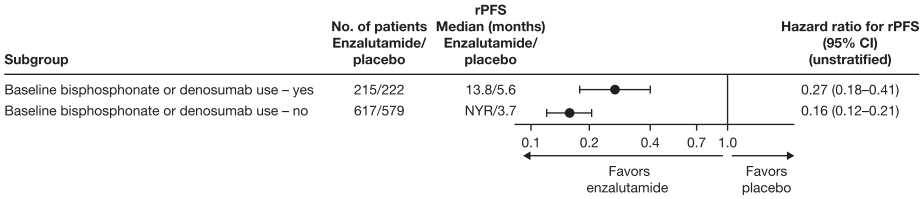

Fig. 2. The effect of enzalutamide treatment, stratified by bisphosphonate use at baseline, on rPFS. Reproduced (with permission) from Beer et al. [42]. CI, confidence interval; HR, hazard ratio; NYR, not yet reached; rPFS, radiographic progression-free survival.

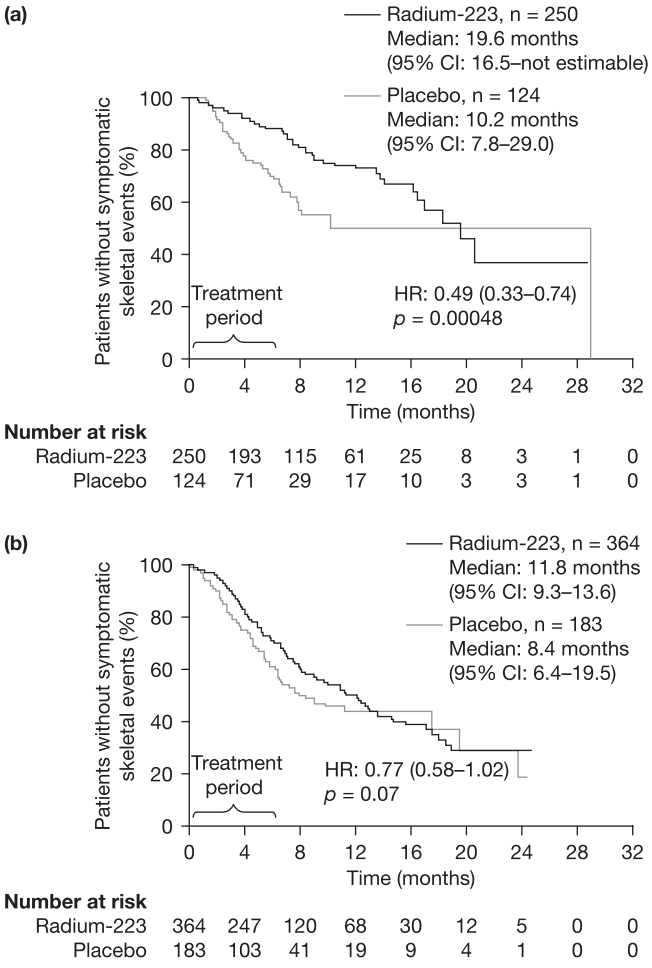

Fig. 3. *Post hoc* effects of radium-223 on symptomatic skeletal events, stratified by (a) bisphosphonate use and (b) no bisphosphonate use at ALSYMPCA study entry. Reproduced (with permission) from Sartor et al. [16]. CI, confidence interval; HR, hazard ratio; radium-223; radium-223 dichloride.

mechanisms of action and toxicity profiles [19]. Clinicians should also consider the most appropriate dose, frequency and duration of treatment and when to initiate specific regimens in order to optimise the use of the new therapies [47]. As yet, there is insufficient prospective scientific evidence to allow a full understanding of the optimal combination of new agents with bisphosphonates or denosumab, the optimal time point at which to initiate treatment, or the optimum duration of combination treatment.

Scientific rationale for combination therapy

The mechanisms of action of new therapies and of bisphosphonates and denosumab are relatively well understood, and they appear to target different aspects of the 'vicious cycle' of bone destruction associated with metastatic prostate cancer (Fig. 5) [3–5,11,12]. This differential targeting may provide a scientific rationale for the possible additive effects on bone health thus far observed with combination therapy.

Enzalutamide, AA and radium-223 primarily target the tumour cells themselves. Despite treatment with medical or surgical castration, tumour growth in men with CRPC can be driven by residual levels of androgens, which may be synthesised by the tumour itself [5,48]. AA is a hormone therapy that acts as a selective, potent and irreversible inhibitor of 17α-hydroxylase/C17,20-lyase (CYP17), which is required for androgen biosynthesis. AA decreases serum testosterone to lower levels than that achieved by ADT or orchiectomy by inhibiting CYP17 in the testicular, adrenal and prostatic tumour tissues [5]. CYP17 inhibition by AA also results in increased mineralocorticoid production by the adrenal glands. In early clinical studies this led to hypokalaemia, fluid retention and hypertension; these events were largely abrogated by coadministration of low-dose glucocorticoids, such as prednisone or prednisolone [5,48,49].

Enzalutamide, another hormone therapy, blocks several steps in the androgen receptor (AR) signalling pathway. It inhibits nuclear translocation of the AR, DNA binding and coactivator recruitment, even in prostate cancer cells that are resistant to ADT [3,41]. Enzalutamide decreases the growth of tumour cells, and can induce cancer cell death and tumour regression [3].

Radium-223 is a radioisotope that has a completely different target from enzalutamide or AA. Radium-223 mimics calcium and selectively targets osteoblasts by forming complexes with the bone mineral hydroxyapatite, specifically in areas of high bone turnover, and emits α-particles [4,6]. These α-particles are directly cytotoxic to the cells that take them up (such as osteoblasts) by inducing double-strand DNA breaks. Damage to the surrounding normal tissue is minimised owing to the short range of the α-particles (< 10 cell diameters) [4,50,51].

Bisphosphonates and denosumab primarily target osteoclasts. Some bisphosphonates, such as ZA, are nitrogen-containing compounds that have a high affinity for mineralised bone. They selectively bind to bone and inhibit farnesyl pyrophosphate synthase; this leads to inhibition of osteoclast differentiation and survival and the stimulation of osteoblasts [12,52]. Denosumab is a fully human monoclonal antibody that selectively binds to RANKL, thereby preventing RANKL from activating its receptor RANK on the surface of osteoclasts and their precursors [11,30,53]. This inhibition by denosumab prevents the maturation of osteoclasts and decreases bone resorption – breaking the 'vicious cycle' of bone destruction.

It is therefore feasible that, with a decrease in tumour burden or activity within the bone microenvironment [38] following treatment with new agents, there are fewer cytokines present or released from the reduced number of tumour cells. Consequently, overall, there could be less stimulation of osteoclasts and less bone resorption leading to less bone destruction, which could result in lower levels of bone pain and a longer time to SREs. The use of bisphosphonates or denosumab in combination with new agents could possibly act in an additive manner to maximise the benefits of the new agents, as shown by *post hoc* findings of an additive effect on OS with concomitant use of denosumab and radium-223 in the early access programme [46]. The additive effects of radium-223 with AA/enzalutamide also observed in the study [46] suggest that further investigation is required to understand the optimum combination of therapies fully in terms of patient benefit–risk. In this regard, it is noteworthy that an increased incidence of death (35% vs 28%) and fractures (26% vs 8%) was identified in asymptomatic or mildly symptomatic patients with chemotherapy-naïve mCRPC who received radium-223 in combination with abiraterone and prednisone/prednisolone compared with those receiving abiraterone plus prednisone/prednisolone during a randomised phase 3 study assessing SSEs [54]. The study was unblinded early as a result of the findings. The EMA has advised physicians to not use this combination in patients with mCRPC until full analysis of the study results is completed [55,56].

Although this hypothesis requires further testing, preclinical and clinical data are beginning to emerge that describe an additional effect of some new therapies on the bone microenvironment, which may offer a rationale for the additive effects of combination therapy. In a recent study conducted *in vitro*, and *in vivo* involving 49 patients with mCRPC, AA was found to have a direct effect on bone anabolism and an antiresorptive effect, as shown by markers of bone turnover, namely an increase in ALP levels and a decrease in serum carboxy-terminal collagen crosslink values, respectively [57]. Based on the established mechanisms of action of bisphosphonates and denosumab on the bone microenvironment, it is feasible that there could be a potential additive effect of AA on osteoclasts and osteoblasts in patients with prostate

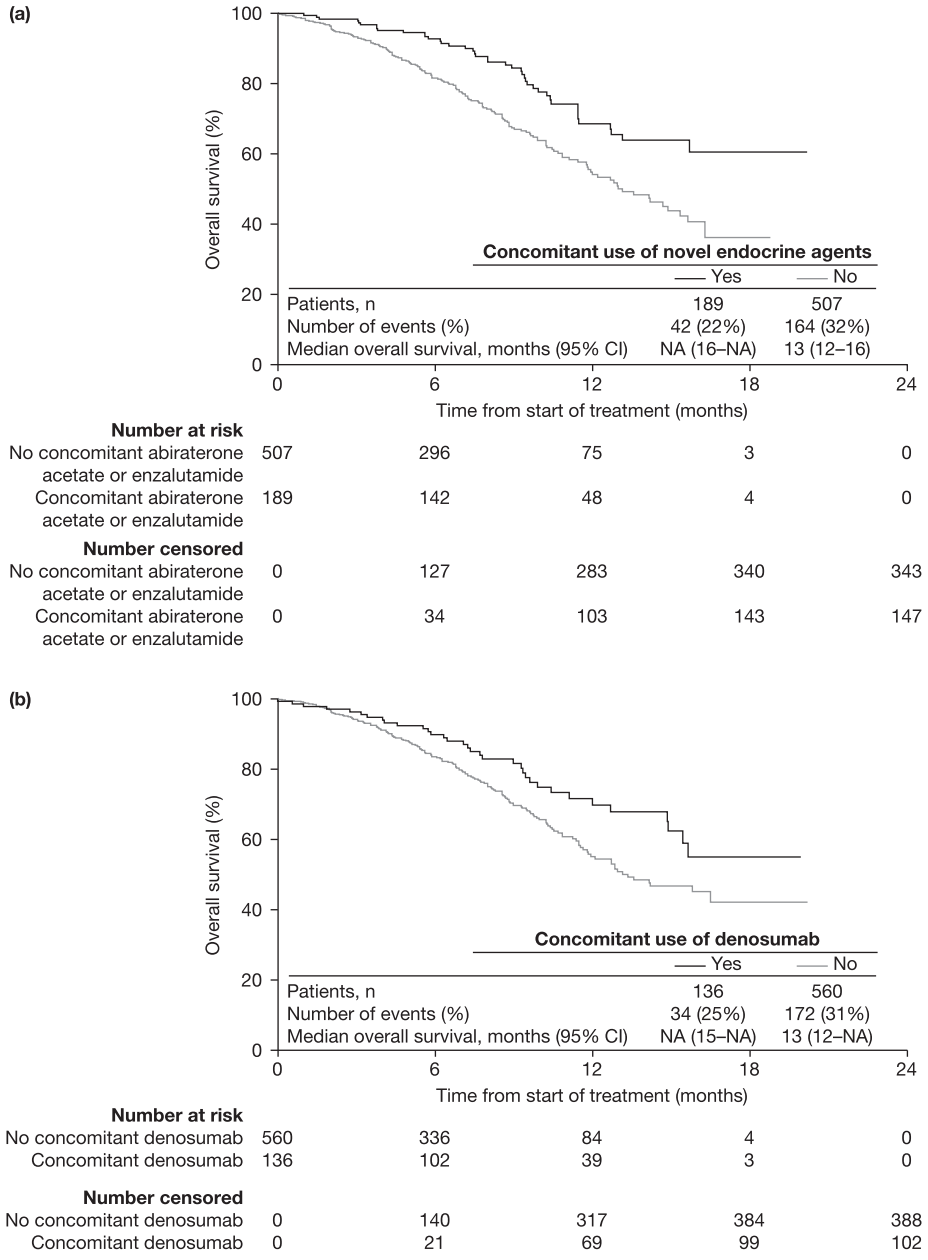

Fig. 4. Kaplan–Meier curves showing overall survival with concomitant use of (a) novel endocrine agents and (b) denosumab in an early access, open-label phase 3b study of radium-223. Reproduced (with permissions) from Saad et al. [46]. In this study, therapy was considered to be concomitant if a novel agent was started after the first injection of radium-223 or if any such agent was administered before the provision of patient informed consent and continued after the first injection of radium-223. CI, confidence interval; NA, not available; radium-223; radium-223 dichloride.

cancer who have bone metastases [57] – in addition to the established efficacy of AA on tumour burden – that could achieve better disease control and management of bone health. Further evidence is required to establish whether similar effects are observed with concomitant use of radium-223 or enzalutamide with bisphosphonates or denosumab.

Safety considerations for combination therapy

In addition to mechanism of action, safety should be considered when combining therapies with bisphosphonates or denosumab. The safety profiles of all the concerned agents are well characterised and, on the whole, are well tolerated by patients [3–5,11,12,41]. AA, enzalutamide, radium-223 and denosumab/ZA have non-overlapping toxicities [3–5,11,12,41,52,58], thus reducing the possibility of serious treatment-emergent adverse events from combination therapy [58].

There are, however, some safety issues of special interest that should be appraised before any potential therapies are combined, and the therapeutic choice may ultimately be driven by patient-specific features (e.g. comorbidities and co-medication) [59]. Both ZA and denosumab are generally well tolerated. Owing to their mechanism of action, hypocalcaemia can occur when treatment is initiated [11,12]. It 'stabilises' thereafter and does not increase with a longer duration of exposure [60]. Supplementation with calcium and vitamin D, pre-treatment correction of low vitamin D and serum calcium levels, and monitoring of serum calcium during treatment are required [11,12,61]. ZA is not recommended for patients with severe renal impairment (creatinine clearance < 30 mL/min) and dose adjustment may be required for patients with mild-to-moderate renal impairment [12]. Denosumab does not need renal dose reduction. However, individuals with severe renal impairment are at risk of developing hypocalcaemia

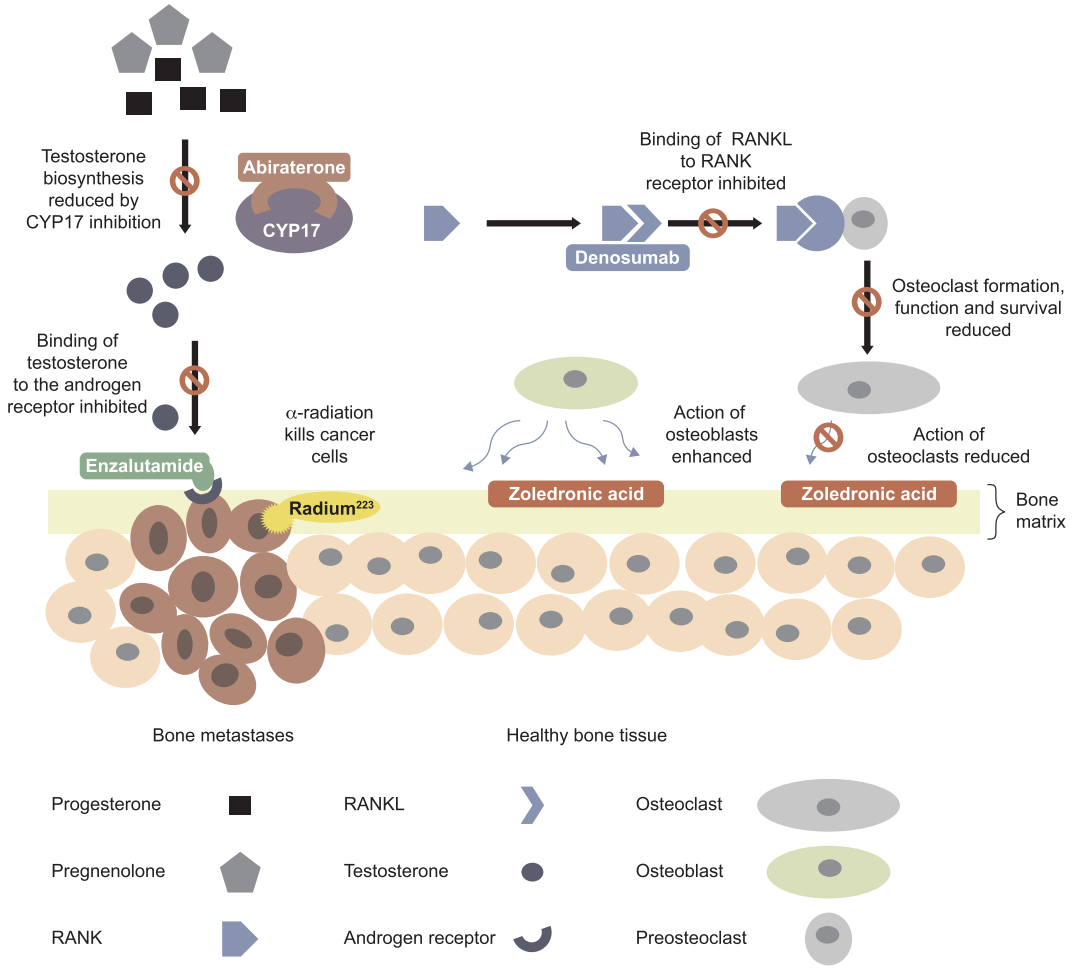

Fig. 5. Mechanism of action of abiraterone acetate, enzalutamide, radium-223 dichloride, zoledronic acid and denosumab on osteoclasts/osteoblasts in the 'vicious cycle' of bone destruction associated with metastasised prostate cancer.

and should be monitored closely [11].

There is a low, but notable, risk of osteonecrosis of the jaw (ONJ) with ZA and denosumab treatment (1.3% and 1.8% in the comparative study, respectively) [62]. The incidence of ONJ increases with time [62], and recent long-term safety findings from the open-label extension phase of the comparative study showed a patient-year adjusted incidence of confirmed ONJ of 1.1% during the first year of denosumab treatment, 3.7% in the second year, and 4.6% per year thereafter [63,64]. Of note, however, is the fact that a small increased risk of ONJ in the oncology population has been associated with concomitant glucocorticoid therapy [62,65–67]. This is of particular interest because ONJ may emerge as a potential, albeit unlikely, problem with long-term AA treatment, which is administered in combination with low-dose prednisone [68]. However, an increase of ONJ associated with AA has not been reported so far, although no specific attention for monitoring ONJ was embedded in the COU-AA-301 or COU-AA-302 trials - in contrast to the pivotal denosumab trials [62].

To reduce the risk of ONJ, the European Society for Medical Oncology (ESMO) guidelines, among others, recommend preventative dental measures before starting treatment, maintenance of good oral hygiene and avoidance of invasive dental procedures during treatment [69]. In the COU-AA-302 study of AA, there was an increased incidence of ONJ with concomitant bisphosphonate or denosumab use compared with no use of these agents. ONJ was reported in < 3% of patients across the treatment groups; all cases were grade 1/2 [14]. A small risk of ONJ was reported with radium-223, with an incidence of 0.6% reported in the ALSYMPCA trial compared with no cases in the placebo group; however, all four patients with ONJ were exposed to prior or concomitant bisphosphonates [4]. The cumulative risk of ONJ would therefore need to be considered when gauging the risk–benefit of combining these therapies with bisphosphonates or denosumab.

Timing and additional considerations for combination therapy

In addition to the appropriate combination of therapies, the point at which treatment with bisphosphonates or denosumab should be initiated during the prostate cancer disease course has yet to be fully determined. There is some evidence to suggest that there is better efficacy of ZA when initiated before the onset of bone pain [70]. However, some physicians wait until the newer hormonal agents have been used and will initiate treatment with bisphosphonates or denosumab only after symptomatic progression has been observed. Some physicians may consider low-dose bisphosphonates or denosumab even before bone metastases are present in order to reduce the risk of osteoporotic fractures. For instance, for patients receiving therapies that may lead to CTIBL (such as ADT), concomitant treatment with these antiresorptive agents, at a lower dose than used in the metastatic setting, may be used to prevent loss of bone [61,71].

As yet, guidelines do not provide recommendations on how to combine bisphosphonates or denosumab with new agents [47,69,72]. The ESMO clinical practice guidelines on bone health in patients with cancer state that antiresorptive agents should be commenced at the time of diagnosis of metastatic bone disease in men with CRPC and should continue indefinitely throughout the course of the disease [69].

Table 3
Ongoing or recently completed combination clinical studies in mCRPC [54,75,80–83].

Trial	Phase	Clinicaltrials.gov identifier	Drugs and trial design	Primary endpoint	Patient population/estimated enrolment (N)/planned study completion date
ERA 223[a]	3	NCT02043678	Randomised, double-blind, placebo-controlled trial of radium-223 in combination with abiraterone acetate and prednisone/prednisolone	Primary: SSE-FS Secondary: OS, time to opiate use for cancer pain, time to pain progression, time to cytotoxic chemotherapy, rPFS, number of patients with AEs	Asymptomatic or mildly symptomatic chemotherapy-naïve patients with bone predominant mCRPC/800/ December 2020
	1	NCT02758132	Pharmacodynamic, open-label trial of denosumab plus enzalutamide, abiraterone acetate and prednisone compared with denosumab plus enzalutamide alone	Primary: serum-based metabolites associated with bone deposition, growth and turnover Secondary: time to SRE, PFS, time to duration of response	CRPC with bone metastases/ recruiting, NA/July 2017
mCRPC-PEACEIII	3	NCT02194842	Randomised, multicentre trial comparing enzalutamide with a combination of radium-223 and enzalutamide	Primary: rPFS Secondary: OS, prostate cancer-specific survival, time to first SSE, time and incidence of first skeletal progression-free, time from entry to initiation of next systemic therapy, treatments elected after first disease progression, second PFS in sequential regimen, pain, time to pain progression, occurrence of AEs, time to first use of opioid analgesics, QoL	Asymptomatic or mildly symptomatic CRPC with metastasis to bone/560/ April 2021
	2a	NCT02034552	Open-label, randomised study evaluating quantified bone scan response following treatment with radium-223 alone or in combination with abiraterone acetate or enzalutamide	Primary: patient bone scan response Secondary: rPFS, SSE-FS, time to first SSE, OS, time to radiological bone progression by treatment group, number of patients with TEAEs, and number of patients with SAEs	Patients with CRPC and bone metastases/66/July 2018
	2	NCT02225704	Interventional trial to determine the safety and tolerability of radium-223 administered in combination with enzalutamide	Primary: safety Secondary: time to clinical and PSA progression, PSA response, time to first SRE, pain assessment, OS	Progressive mCRPC/44/December 2017 (for completion of the primary outcome measure)
eRADicAte	2	NCT02097303	Open-label, phase 2 trial of radium-223 with concurrent administration of abiraterone acetate plus prednisone	Primary: efficacy assessed by bone pain assessments and QoL questionnaires Secondary/other: safety, time to SREs, time to PSA progression, progression to additional antineoplastic therapy, performance status	Symptomatic CRPC with bone metastases/40/August 2016

AE, adverse event; CRPC, castration-resistant prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; NA, not available; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen, QoL, quality of life; rPFS, radiological progression-free survival; radium-223; radium-223 dichloride; SAE, serious adverse event; SRE, skeletal-related event; SSE, symptomatic skeletal event; SSE-FS, symptomatic skeletal event-free survival; TEAE, treatment-emergent adverse event.

[a] Study was unblinded early due to an increased incidence of deaths and fractures in patients who received radium-223 in combination with abiraterone acetate and prednisone/prednisolone.

The combination of these agents with new therapies is not yet considered in these guidelines [69]. Guidelines from the St Gallen Advanced Prostate Cancer Consensus Conference for the management of patients with mCRPC recommend that the majority of men with CRPC with bone metastases should receive an osteoclast-targeted agent for the prevention of SREs [47]. However, these guidelines report that the optimal timing for starting such osteoclast-targeted treatment, optimal treatment intensity (dose and frequency) and optimal treatment duration in men with CRPC is unclear [47].

Despite the lack of guidelines, evidence from real-world studies is emerging regarding the concurrent use of bisphosphonates or denosumab and new therapies [73]. Real-world treatment patterns of bisphosphonates or denosumab use across six EU countries have indicated that 74% (n = 1454) of 1971 patients with advanced prostate cancer and bone metastases were receiving one of these agents. A large proportion of patients given a novel therapy were receiving concurrent treatment with bisphosphonates or denosumab: 75% (n = 335/449) of patients receiving AA, 67% (n = 99/148) of those receiving enzalutamide and 70% (n = 7/10) of those receiving radium-223 [73].

Ongoing clinical studies investigating combinations of new agents are likely to provide additional useful information for physicians considering optimal treatments for patients (Table 3). The ongoing phase 3, double-blind, placebo-controlled ERA 223 study (ClinicalTrials.gov identifier: NCT02043678) is researching the combination of radium-223 and AA with prednisone/prednisolone in the treatment of approximately 800 asymptomatic or mildly symptomatic chemotherapy-naïve men with bone-predominant mCRPC. SSE-free survival is the primary endpoint and patients will be stratified by with or without concurrent use of denosumab or bisphosphonates [74]. As mentioned earlier in this review, the ERA 223 trial was unblinded early due to an imbalance in the incidence of deaths and fractures in patients who received radium-223 combination therapy [54–56]. The phase 3 PEACE III study (ClinicalTrials.gov identifier: NCT02194842) may help to understand if there is a beneficial effect of using a bone-targeted agent with radium-233 [75]. In this study, comparing radium-233 plus enzalutamide with enzalutamide alone in asymptomatic or mildly symptomatic mCRPC, the use of a bone-targeted agent to reduce the risk of fractures and other SREs is recommended in all patients entering the study. Finally, a small study (ClinicalTrials.gov identifier: NCT02758132) is recruiting patients to investigate the combination of denosumab plus enzalutamide, AA and prednisone, versus denosumab plus enzalutamide, in men with mCRPC to characterise serum metabolites associated with bone deposition, growth and turnover.

This review focuses on men with CRPC and bone metastases. However, data are lacking on the use of new agents in combination with bisphosphonates or denosumab in patients with hormone sensitive prostate cancer (HSPC). A randomised controlled trial investigating the use of ZA in men receiving ADT for HSPC (CALGB 90202) found no significant benefits from the use of the bisphosphonate in terms of time to first SRE or OS [76]. Results of the multistage, open-label, randomised controlled Systemic Therapy in Advancing or Metastatic Prostate cancer: Evaluation of Drug Efficacy (STAMPEDE) study have indicated that, although well-tolerated, the addition of ZA to ADT in men with HSPC conferred no survival benefit, and no decrease in SREs; by contrast, the addition of docetaxel to ADT was beneficial in terms of OS and in preventing SREs [77]. The lack of evidence for using bisphosphonates in HSPC could reflect the low rate of SREs in this setting, and the consequent challenges with obtaining sufficient data to show an effect.

More recently, the STAMPEDE authors reported clinically and statistically significant improvements in OS and failure-free survival in men with HSPC receiving AA and prednisolone in addition to ADT (compared to ADT alone, with a manageable increase in toxicity [78]. A significant increase in the proportion of patients without SSEs over a 3-year period was reported for the AA plus ADT arm, versus the ADT alone arm [78]. The number of grade 3–5 events was, however, higher in the combination arm (47% vs 33%). The results from the first interim analysis of the LATITUDE trial of AA and prednisone added to ADT in men with newly diagnosed high-risk metastatic HSPC reported significant improvements in men randomised to add-on AA (vs placebo) in terms of OS, rPFS and all secondary endpoints, including time to next SSE. Despite an increase in Grade 3/4 adverse events (hypertension, hypokalemia, increased ALT or AST) in the add-on AA (vs placebo) treatment arm, the ethics committee have recommended unblinding and crossing all placebo/ADT patients over to AA/ADT [79].

Future perspectives

In conclusion, the addition of bisphosphonates or denosumab to new therapies has the potential to provide clinical benefits for men with prostate cancer and bone metastases and there is evidence of an additive effect between these agents and the new therapies. However, this is based largely on *post hoc* data from clinical trials, which have limitations. Further evidence is therefore required from clinical studies and the real-world setting to enable physicians to understand the efficacy and safety of combination therapy with new agents and bisphosphonates or denosumab. Given the current evidence gaps, a randomised study to demonstrate prospectively the benefits of combining new therapies with these inhibitors of bone resorption could be designed on the basis of currently available data in order to inform clinicians further.

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CNS has received research funding for her department or has consulted with: Astellas, Bayer, Clovis, Ferring, Ipsen, Janssen, Medivation, Roche/Genentech and Sanofi Genzyme.

PFAM has been a consultant for Astellas, AstraZeneca, Bayer, GSK, J &J, Novartis, Pfizer, participated in clinical trials Astellas, Dendreon, GSK, J&J, Millennium, Pfizer and received grants/research supports from Astellas, Bayer, GSK, Pfizer, Wilex.

DN is an employee of Amgen and holds stock.

BT has been an advisor and an investigator for Amgen, Astellas, Medivation, Janssen, and Sanofi.

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