Bone health and therapeutic agents in advanced prostate cancer

Maria Antonia Gómez-Aparicio1, Fernando López-Campos2,*, Lira Pelari-Mici2, David Buchser3, Jorge Pastor4, Xavier Maldonado5, Juan Zafra6, Alison C. Tree7, Renée Bultijnck8, Paul Sargs9, Piet Ost10, Felipe Couñago11

1Department of Radiation Oncology, Hospital Universitario de Toledo, 45007 Toledo, Spain
2Department of Radiation Oncology, Hospital Universitario Ramón y Cajal, 28034 Madrid, Spain
3Department of Radiation Oncology, Hospital Universitario Cruces, 48903 Barakaldo, Spain
4Department of Radiation Oncology, ASCIRES Hospital General Universitario de Valencia, 46014 Valencia, Spain
5Department of Radiation Oncology, Hospital Vall d’Hebron, 08035 Barcelona, Spain
6Department of Radiation Oncology, Hospital Universitario Virgen de la Victoria, 29010 Malaga, Spain
7Department of Radiation Oncology, The Royal Marsden Hospital and Institute of Cancer Research, SM2 5PT Sutton, UK
8Department of Radiation Oncology, Ghent University Hospital, 9000 Ghent, Belgium
9Department of Radiation Oncology, Institut Bergonié, 33000 Bordeaux, France
10Department of Radiation Oncology, Iridium Network, 2610 Antwerp, Belgium
11Department of Radiation Oncology, Hospital Universitario Quironsalud, Hospital La Luz, Universidad Europea de Madrid, 28223 Madrid, Spain

*Correspondence: flcampos@salud.madrid.org (Fernando López-Campos)

Academic Editors: Guohui Sun and Graham Pawelec

Submitted: 28 October 2021 Revised: 8 December 2021 Accepted: 15 December 2021 Published: 18 January 2022

Abstract

Prostate cancer is the most frequent genitourinary tumor worldwide. Maintaining an optimum bone health throughout the natural course of prostate cancer is an important aspect in the management of this disease, particularly in this at risk population of older and frail patients who experience bone loss related to androgen-deprivation therapy (ADT) and/or patients who develop bone metastases. The number of treatment options for advanced prostate cancer that combine ADT with docetaxel, new hormonal agents and/or radiotherapy has increased substantially in recent years. Bisphosphonates and other bone targeted agents such as denosumab have shown an improvement in bone mineral density and are suited for patients with treatment-related osteoporosis and/or bone metastases with an increased risk of skeletal-related events (SREs). In this context, the aim of this review is to analyse key aspects of bone health and therapies that can prevent the occurrence of SREs throughout the clinical course of prostate cancer, and how to combine them with new available treatments in this setting.

Keywords: Bone health; Prostate cancer; Skeletal-related events; Osteoporosis; Denosumab; Bisphosphonates

1. Introduction

Prostate cancer (PCA) is the most frequent solid tumor in males and androgen-deprivation therapy (ADT) plays an important role in its treatment, both as part of definitive therapy and in advanced or metastatic stages, where it continues to be a first line treatment. It is estimated that 50% of patients with PCA will receive ADT at some point during the natural history of their disease [1].

It is widely known that the use of ADT is associated with osteopenia, which can evolve into osteoporosis, and an increased risk of fracture. This deficit in mineralization is related to a reduction in testosterone levels and a reduced aromatization of estrogens, which are important factors in bone health [2]. Osteopenia occurs in up to 85% of cases and osteoporosis ranges, according to different studies, between 9–53% [2,3]. The magnitude of this osteopenia is associated with the duration of androgen suppression (among other factors), although several studies show that the most important loss in bone mineral density (BMD)—up to 10% depending on the location—occurs during the first year of ADT [1,3,4]. After this year, the rate of BMD loss slows down to approximately 2% per year, which still represents between twice and four times the physiological loss in the general male population. Consequently, the risk of fracture over the following 5 years increases from 12.6% in untreated patients to 19.4% in those who receive ADT, with the subsequent impact in quality of life and survival [5,6].

For all the above reasons, it is important to conduct a proper evaluation to establish preventive measures. However, according to the results of a Canadian study evaluating ADT management, only 58.8% of patients had a basal densitometry and only 20.3% were re-evaluated during follow-up, which led to undertreatment (only 13% were treated with bisphosphonates) [3].

PCA tends to metastasize in the bones. Tumor cells usually secrete promoting factors of bone formation, such as bone morphogenetic proteins (BMPs) and RANK-L inhibitors, which attenuate osteoclastic activity. This is the reason why most bone metastases are osteoblastic, although mixed, osteolytic or even metastases with no radiological evidence are reported in the literature.
These lesions frequently generate pain and skeletal-related events (SREs) that can be caused by secondary osteopenia due to prolonged ADT use or by pathologic fractures secondary to a bone metastasis. The accumulated incidence of these SREs in the following two years after the diagnosis of metastatic PCA is 41.9% [7].

Bisphosphonates and drugs that target osteoclast receptors such as denosumab, in addition to calcium and vitamin D supplements, play an important role in the prevention and reduction of osteopenia/osteoporosis in patients with bone metastases and in those receiving ADT [8,9]. The treatment options for advanced PCA that act on bone metastasis by combining ADT with docetaxel, new hormonal agents and/or radiotherapy have substantially increased in the last few years and highlight the necessity of an adapted bone protection strategy [10].

The aim of this review is to analyze the correct assessment of bone health, as well as the main targeted treatments and their association with specific oncological treatments for PCa patients.

2. Bone health assessment and prevention

2.1 Bone health assessment in the management of patients with PCa

Bone tissue is subjected to a continuous process of remodeling based on the coordinated generation and resorption mediated by osteoblasts and osteoclasts, respectively. Osteoclast activity is regulated, among other factors, by the receptor activator of nuclear factor κB (RANK) and osteoprotegerin (OPG). The union of RANK with its ligand (RANKL) favors the survival of osteoclasts, whereas the union of RANK with OPG inhibits their activity. Therefore, BMD depends on a cellular and molecular balance.

Osteoporosis is a metabolic bone dysfunction defined by the loss of bone tissue and the deterioration of its microarchitecture. The physiology of bone remodeling is mediated by multiple cytokines and hormones. Estrogens inhibit bone resorption, whereas androgens promote bone formation. An alteration in this balance explains why this group of patients has a loss of BMD and the onset or worsening of osteoporosis [11].

Osteoporosis induced by ADT can be severe: it causes an important deficit in BMD during the first 6–12 months of treatment, 17.3% higher than males untreated for PCa, and it is associated with a higher risk of fracture [12]. The prevalence of osteoporosis in this group of patients varies between 10–40% and increases with age and ADT duration [13,14]. This reinforces the importance of conducting an adequate evaluation to prevent BMD deficit in all patients that are going to start treatment with ADT [14].

The use of ADT in addition to other systemic treatments in more advanced stages of PCa, such as next generation anti-androgens, glucocorticoids or radium-233 (Ra-233) results in increased bone resorption and, consequently, decreased BMD [15,16], which translates into a higher risk of suffering SREs [17]. Moreover, bone metastasis related to PCa poses a higher risk of pathologic fractures. It is important to identify those patients at risk given that it has already been reported in multiple clinical trials that the combination of bone-targeted therapies and different treatments for advanced PCa have a positive impact both in pain control and reduction of SREs [18–20].

Before any treatment for PCa is started, the assessment of BMD is useful for identifying those patients with osteopenia or osteoporosis and for establishing the risk of fracture. There is a direct and progressive association between the loss of BMD and fractures, as the risk doubles for each decrease in standard deviation [21]. The basic tool for evaluating BMD is bone densitometry through a dual energy X-ray absorptiometry of the femoral neck.

The World Health Organization establishes a cut-off point to define osteoporosis (and therefore a high risk of fracture) of 2.5 standard deviations below the average of a female young adult (T-score ≤2.5), and the same is used for males [22]. Although BMD assessment has high specificity for risk of fracture, its sensitivity is low [23]. For this reason, it is recommended to complement the information provided by bone densitometry with clinical risk factors. There is a well-established association between the risk of bone fracture and other SREs, with the following risk factors: age >65, body mass index (BMI) <24, tobacco, alcohol, previous history of falls and fractures, and family history of hip fracture [24].

To help with the evaluation and decision-making in this clinical scenario, various tools have been developed as algorithms that calculate the risk of fracture from a series of risk factors exclusively or with the addition of BMD. For instance, the Fracture Risk Assessment Tool (FRAX) is an algorithm that provides an estimation of the 10-year risk of osteoporotic fracture for each person, with the advantage of being validated for independent cohorts in several countries [25].

Despite the obvious importance of assessing bone health in patients with PCa, there are no clearly established cut-off points to guide the start of bone-targeted therapies or standard intervals to conduct tests during follow-up.

Briot et al. [26] published a series of recommendations to evaluate which patients with PCa under ADT have a risk of fracture and, therefore, would be candidates for treatment with bone-protecting agents (BPA). They propose the evaluation of BMD before the start of ADT and recommend the prescription of antiresorptive therapy if T score <−2.5 or between −1.5 and 2.5 with concurrent factors such as BMI <19, age >75 years, cardiovascular disease, or frequent falls [26]. Furthermore, European guidelines on the treatment of genitourinary tumors recommend treatment with antiresorptive therapy if the annual bone loss is >5% in patients receiving ADT [27].
A reasonable approximation to assess bone health in PCa patients and the start of BPA is the proposal of the European Association of Medical Oncology (ESMO), an adaptation of the recommendations by Hadji et al. [28, 29] or women under aromatase inhibitors (Fig. 1, Ref. [29]).

Because the FRAX score is not well optimized for PCa patients on ADT, some centres proactively start Vitamin D and bisphosphonates in all patients receiving long term ADT. Studies show that 77% of men on ADT exceed the FRAX threshold for prophylactic therapy hence population based therapy is likely to be of benefit [30].

2.2 Prevention and therapeutic strategies

2.2.1 Physical exercise

Experts recommend physical activity in patients with cancer due to its numerous health benefits. While there is no solid evidence that it specifically prevents the loss of BMD and the risk of fracture in patients receiving ADT [31], it is an effective strategy for generating significant benefits in general health.

Furthermore, exercise also has a positive impact on other ADT-induced side effects such as obesity and sarcopenia, which are also known risk factors for bone health.

The European Association of Urology (EAU), ESMO and the National Comprehensive Cancer Network (NCCN) guidelines also prescribe following other lifestyle changes; smoke cessation, limitation of alcohol intake and healthy weight due to their known impact on bone health [27, 28, 32].

2.2.2 Calcium and vitamin D supplements

The adequate intake or supplementation of calcium and vitamin D in patients receiving ADT supplements is reflected in clinical guidelines [28, 33]. Studies that employ densitometry for patient evaluation have reported that these supplements attenuate the loss of BMD during ADT, especially during the first year [34]. However, there is no trial to date that has compared the intake of supplements vs. placebo in patients with non-metastatic PCa receiving ADT.

The EAU, NCCN and ESMO recommend the supplementation of vitamin D deficit in patients under ADT: 800–1000 UI/day of vitamin D3 and 1000–1200 mg/day of calcium (from food and supplements). This prescription should be continued if introducing BPA [35]. Currently, there are no guidelines on the frequency of vitamin D level testing.

2.2.3 Bone-protecting agents

Bisphosphonates are pyrophosphate analogues. They inhibit the effect of prostacyclins and cytokines in the bone tissue and reduce the number of osteoclasts through the
downregulation of the reticuloendothelial system, thus preventing bone resorption by inducing the apoptosis of osteoclasts. Bisphosphonates include zoledronic acid (ZA), ris- dronate, pamidronate, ibandronate, alendronate, etidronate and clodronate, with ZA being the most employed intra- venously (iv) in PCa patients.

Denosumab is a human monoclonal antibody (IgG2) that binds to RANKL with great affinity and specificity. RANKL is expressed as a soluble or transmembrane protein and is essential in the formation, function and survival of os- teoclasts, the only cell responsible for bone resorption. The increase in osteoclastic activity stimulated by RANKL is a key mediator of bone destruction in metastatic disease. The union of denosumab to RANKL prevents RANKL-RANK interaction, thus blocking the transduction signal that stim- ulates the formation, activation, and survival of osteoclasts. This agent is administered subcutaneously.

Both bisphosphonates and Denosumab are well tolerat- ed. Except for the acute reaction that can be caused by the iv administration of ZA, side effects are rare if follow- ing the recommended dose and treatment schedule. Special precautions should be taken regarding the renal toxicity of ZA: a dose reduction is advised with a baseline creatinine clearance of 30 to 60 mL/min and should not be adminis- tered if >30 mL/min [28]. Electrolyte imbalance is asso- ciated with both treatments, with hypocalcemia being more common with denosumab [10]. Denosumab can produce mandibular osteonecrosis, whereas no differences in the in- cidence of this side effect are observed when comparing ZA to placebo [36], therefore, a dental evaluation is rec- ommended before the start of antiresorptive agents.

In terms of toxicity in patients receiving treatment with these drugs while receiving ADT and with no bone metastases, no cases of mandibular osteonecrosis have been reported in clinical trials [9,37,38].

3. Prevention of osteoporosis and bone metastases in non-metastatic locally advanced prostate cancer

3.1 Non-metastatic hormone-sensitive prostate cancer

In this scenario, various trials have evaluated the role of ZA and have found a benefit in the protection from osteo- porotic events induced by ADT and the increase in BMD. However, no differences have been reported in terms of pre- vention of fractures or quality of life. For this reason, ZA is not approved for this specific setting and its use depends on the clinical judgement of the prescribing physician. The doses in these studies were 4 mg every 3 or 12 months [37– 40]. However, a dose of 5 mg annually is recommended as a professional consensus [26]. Oral BPA may be considered as an alternative.

Denosumab is the only drug approved by the Food and Drug Administration and the European Medicines Agency for the prevention of pathologic fractures caused by os- teoporosis in patients under ADT. In the pivotal trial that led to this approval, after a follow-up of 36 months, pa- tients treated with denosumab presented less vertebral frac- tures and an increase in BMD in comparison to the placebo group, with statistically significant differences in both cases [9]. The recommended dose in this setting is 60 mg subcu- taneously every six months.

3.2 Non-metastatic castration-resistant prostate cancer

Treatment for patients with non-metastatic castration- resistant prostate cancer (nmCRPC) has drastically changed with the introduction of next generation inhibitors of the androgen receptor. These drugs were approved after show- ing a significant increase in metastasis-free survival (MFS) compared to placebo in three randomized phase III clinical trials [41–43]. The results of these three studies suggest that, in patients with nmCRPC these new agents are highly effective at postponing development of metastases. In all three trials the percentage of patients with added treatment with bone-targeted therapies was low: 11% (enzalutamide) vs. 10% (placebo) in PROSPER, 10.2% vs. 9.7% in SPAR- TAN and 3% vs. 6% in ARAMIS. Therefore, no conclu- sions can be drawn on the concomitant treatment with both therapies.

The benefit of denosumab has been investigated in a phase III clinical trial that included 1432 patients with CRPC. Of these, 716 were nmCRPC and were treated with a monthly dose of 120 mg of subcutaneous denosumab. A significant increase in MFS was observed when compared to placebo (29.5 vs. 25.2 months; hazard ratio (HR): 0.85; \( p = 0.028 \)). However, this was at the expense of mandibu- lar osteonecrosis in 5% of participants, which explains why denosumab is not currently approved for the prevention of metastasis in this subset of patients [44].

Regarding bisphosphonates, although preclinical data suggest their antitumor activity, they have not shown a de- crease in the appearance of bone metastases in this subgroup of patients [45].

4. Prevention of skeletal-related events in metastatic prostate cancer

4.1 Metastatic castration-resistant prostate cancer

ZA is the only bisphosphonate that has demonstrated a reduction in SREs related to bone metastases in men with metastatic castration-resistant prostate cancer (mCRPC) [28]. Saad et al. published the results of a multicenter ran- domized trial that compared ZA vs. placebo in this group of patients. The evaluated dose was 4 mg every three weeks and 8 mg every three weeks (which was later reduced to 4 mg) against placebo. Patients in the placebo group had more SREs than those treated with 4 mg (\( p < 0.021 \)) or 8 mg/4 mg of ZA. Pain and need of analgesia were higher in the placebo group, but no differences were found in dis- ease progression, performance status or quality of life. This study defined the tolerance profile of ZA, with 4 mg be- ing the optimal dose compared with 8 mg [46]. After 24
months of treatment, the annual incidence of SREs was significantly higher in the placebo group ($p < 0.005$). Median time to the first SRE was reached in both groups, being six months longer for ZA ($p < 0.009$) [47]. In further analyses, it was observed that ZA reduced the percentage of patients with ≥1 SREs and delayed the onset of bone pain in patients who were asymptomatic at the start of the study [48–50]. ZA also showed a non-statistically significant tendency towards a prolonged overall survival (OS) in patients with mCRPC [51].

Pan et al. [52] evaluated the efficacy and safety of the combination of ZA and docetaxel in CRPC with bone metastases in a prospective study of 105 patients. The combined treatment presented better OS ($p = 0.02$) and bone MFS ($p < 0.05$) than docetaxel and placebo, with no differences in toxicity [52]. Furthermore, TRAPEZE trial suggested that ZA could have a role as maintenance therapy after docetaxel due to an improved interval free of SRE, mainly after disease progression [53].

Between these two treatments, denosumab has demonstrated to be superior to ZA in patients with bone metastases [54]. Fizazi et al. [10] published the results of a double-blinded, randomized study in patients with mCRPC. 120 mg of subcutaneous denosumab every four weeks were superior to 4 mg of iv ZA. Denosumab significantly reduced the risk of appearance of a first SRE and posterior skeletal events compared to ZA ($p < 0.008$), although no differences in OS were observed. In a subanalysis, denosumab showed a benefit in the delay of pain progression compared to ZA by increasing the time to the onset of moderate-severe pain ($p < 0.0001$) (Table 1) [55].

It is recommended to start ZA or denosumab in patients with CRPC and bone metastases, even if they are asymptomatic, in doses of 4 mg of iv ZA every four weeks and 120 mg of subcutaneous denosumab every month [56].

Regarding other treatments available in mCRPC, Ra-223 is an alpha emitter radionucleotide tailored for the treatment of patients with osteoblastic metastases, with benefits in OS and SREs, and manageable side effects. Various trials have studied its combination with BPA and/or next generation anti-androgens [57].

The ERA 223 trial combined abiraterone plus prednisone with Ra-223 or placebo in patients with mCRPC who had not received previous chemotherapy [17]. The study showed, contrary to expectations, that the addition of Ra-223 did not improve SRE-free survival and was, in fact, associated with a higher risk of fracture, mainly in bone sites with no metastases. However, post-hoc analysis showed that the increase in bone fractures was particularly observed in patients not receiving BPA. These findings reinforce the importance of adequate monitoring bone health and the use of BPA [58]. These results are not replicated with the combination of enzalutamide and Ra-223 as the results of ERA 223 trial has led to the mandatory use of BPS in the phase III EORTC-1333/PEACE III trial, which treats patients with Ra-223 plus enzalutamide vs. enzalutamide alone. An interim safety analysis was performed and confirmed that, in absence of BPA, fracture risk was increased and, more importantly, the risk remains almost nonexistent with a preventive continuous administration of BPA. Again, this highlights the value of BPA in this patient population [57].

There are data that support the concomitant administration of Ra-223 with osteoclast-targeted agents. The phase III study ALSYMPCA recruited 921 patients with mCRPC with symptomatic bone metastasis and no visceral lesions and randomized them to receive 50 KBq/Kg of Ra-223 every four weeks or placebo [59]. OS, the primary endpoint of this study, was reported as 14.9 months in the experimental arm vs. 11.3 in the placebo arm (HR: 0.70; $p < 0.001$). 41% of patients received bisphosphonates and a delay in the onset of SREs was observed in this subgroup (19.6 vs. 10.2 months; HR: 0.49; $p = 0.00048$). At present, international guidelines recommend that, in men with mCRPC previously treated with docetaxel (or unsuitable for docetaxel) and one anti-androgen and who present bone pain, Ra-223 should be considered as a treatment option to prolong life, reduce symptomatic SREs and improve quality of life. Concomitant use with abiraterone and prednisone is advised against due to an increased risk of fracture [60].

As for the new anti-androgens, a post hoc analysis of the COU-AA-302 trial reported that, in patients with no previous chemotherapy, bone-directed therapies administered concomitantly with abiraterone and prednisone were associated with improved clinical results compared to previous studies in terms of OS, time to worsening in performance status and pain control [18]. Likewise, the PREVAIL study reported a 29% reduction in the risk of death and prolonged time to the first SRE in patients with no previous chemotherapy who received enzalutamide [61].

4.2 Metastatic hormone-sensitive prostate cancer

ZA has been evaluated in patients with metastatic hormone-sensitive prostate cancer (mHSPC). In the STAMPEDE trial, the addition of ZA to standard of care (SOC) treatment was not associated with an improvement in OS, disease free survival or delay in SRE [19]. Similar results were obtained in the CALGB 90202 study, which evaluated ADT plus ZA versus ADT plus placebo, and found no differences in the time to the first SRE, OS or grade ≥3 toxicity [62]. The ZAPCA trial also reported comparable results [63] (Table 1). There are still no published data on the role of denosumab in this setting.

For the reasons above, the use of ZA or denosumab is not approved for clinical practice in mHSPC for purposes of disease control.

In contrast, several clinical trials have shown benefits in OS and radiographic progression-free survival (rPFS) associated with next generation hormonal therapies [64–67]. The ARCHES trial [58] and the ENZAMET trial laid the
## Table 1. Randomized studies with zolendronic acid and denosumab in mCRPC and mHSPC.

| Study/author name | Study population | Treatment arms | Primary endpoints | Results |
|-------------------|------------------|----------------|------------------|---------|
| Saad             | mCRPC            | ZA 4 mg/3 weeks vs. placebo | SRE          | ZA reduced SRE compared to placebo, \( p = 0.021 \) |
| Fizazi           | mCRPC            | Denosumab 120 mg/4 weeks vs. ZA 4 mg/3 weeks | Time to first SRE | Median time to first SRE and further SREs was superior with denosumab \( p < 0.008 \) |
| TRAPEZE          | mCRPC            | Docetaxel + prednisolone vs. Docetaxel + prednisolone + ZA vs. Docetaxel + prednisolone + strontium-89 vs. Docetaxel + prednisolone + ZA + strontium-89 | CPFS (pain progression, SRE or death) | ZA did not improve CPFS, but delayed the time to first SRE |
| STAMPEDE         | mHSPC            | SOC vs. ZA + SOC vs. SOC + docetaxel vs. SOC + ZA + docetaxel | Overall survival | ZA did not improve overall survival or delayed the appearance of metastasis |
| CALGB 90902      | mHSPC            | ZA 4 mg/4 weeks vs. placebo | Time to first SRE | No differences in time to SRE or survival |
| ZAPCA            | mHSPC            | ZA + ADT vs. ADT | Time to treatment failure and time to first SRE | Time to first SRE longer in ZA + ADT \( p < 0.009 \) |

mCRPC, metastatic castration-resistant prostate cancer; ZA, zolendronic acid; SRE, skeletal-related events; CPFS, clinical progression-free survival; mHSPC, metastatic hormone-sensitive prostate cancer; SOC, standard of care; ADT, androgen-deprivation therapy.

## Table 2. Selected clinical trials of bone modifying agents alone or in combination with second generation hormonal treatments in prostate cancer.

| NCT number | Study type | Name                                                                 | Primary endpoint                                      | Secondary endpoints                                      | Estimated enrollment | Stage |
|------------|------------|----------------------------------------------------------------------|--------------------------------------------------------|----------------------------------------------------------|----------------------|-------|
| NCT03732820 | Phase 3    | A Randomised, Double-blind, Placebo-controlled, Multicentre Phase III Study of Olaparib Plus Abiraterone Relative to Placebo Plus Abiraterone as First-line Therapy in Men With Metastatic Castration-resistant Prostate Cancer (PROpel Study). | ● Radiological progression-free survival (rPFS) | ● Overall survival (OS) ● Time to first subsequent anti-cancer therapy or death (TFST) | 904                  | Recruiting |
| NCT04050397 | -          | Exercise Intervention to Reduce Adverse Quality of Life Effects From Androgen Deprivation Therapy for Prostate Cancer - Randomized Clinical Trial. | ● Overall quality of life ● Prostate cancer-specific quality of life | ● Bone fractures ● Time to prostate cancer death | 40                   | Recruiting |

(…)

6
| NCT number  | Study type | Name                                                                 | Primary endpoint                                                                 | Secondary endpoints                                                                 | Estimated enrollment | Stage          |
|------------|------------|----------------------------------------------------------------------|----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|----------------------|---------------|
| NCT04507698 | Phase 3    | INTense Exercise foR surVivAL Among Men With Metastatic Castrate-Resistant Prostate Cancer (INTerval - MCRPC): A Multicentre, Randomised, Controlled, Phase III Study. | • Overall Survival                                                                | • Disease progression                                                                | 80                   | Recruiting    |
|            |            |                                                                     |                                                                                  | • Symptomatic Skeletal Related Events                                               |                      |               |
|            |            |                                                                     |                                                                                  | • Analgesic/Opiate Use                                                              |                      |               |
|            |            |                                                                     |                                                                                  | • (…)                                                                              |                      |               |
| NCT04549207 | Phase 4    | A Randomised Trial Comparing Continuation or De-escalation of Bone Modifying Agents (BMA) in Patients Treated for Over 2 Years for Bone Metastases From Either Breast or Castration-resistant Prostate Cancer (REaCT-Hold BMA). | • Health related quality of life scores                                             | • Symptomatic Skeletal Event (SSE)                                                   | 240                  | Recruiting    |
|            |            |                                                                     |                                                                                  | • Time to development of Symptomatic Skeletal Event                                 |                      |               |
|            |            |                                                                     |                                                                                  | • Symptomatic Skeletal Event-free survival                                          |                      |               |
|            |            |                                                                     |                                                                                  | • Skeletal morbidity                                                                |                      |               |
|            |            |                                                                     |                                                                                  | • (…)                                                                              |                      |               |
| NCT02051218 | Phase 3    | Prevention of Symptomatic Skeletal Events With Denosumab Administered Every 4 Weeks Versus Every 12 Weeks - A Non-Inferiority Phase III Trial. | • Time to first on-trial symptomatic skeletal event                                 | • Toxicity (focus on hypocalcemia and osteonecrosis of the jaw)                     | 1181 (actual enrollment) | Active, not recruiting |
|            |            |                                                                     |                                                                                  | • Time to first and subsequent on-trial SSE                                         |                      |               |
|            |            |                                                                     |                                                                                  | • Quality of Life                                                                   |                      |               |
|            |            |                                                                     |                                                                                  | • (…)                                                                              |                      |               |
| NCT03869762 | Phase 2    | A Phase II Study of Denosumab in Combination With Enzalutamide in Progressive Metastatic Castrate-resistant Prostate Cancer and Bone Metastases. | • Radiographic progression-free survival (rPFS)                                  | • Overall survival                                                                   | 6 (actual enrollment) | Suspended     |
|            |            |                                                                     |                                                                                  | • PSA progression free survival                                                     |                      | (Insufficient accrual) |
|            |            |                                                                     |                                                                                  | • Time to first skeletal-related event                                               |                      |               |
|            |            |                                                                     |                                                                                  | • Pain assessment                                                                   |                      |               |
| NCT02194842 | Phase 3    | A Randomized Multicenter Phase III Trial Comparing Enzalutamide vs. a Combination of Ra223 and Enzalutamide in Asymptomatic or Mildly Symptomatic Castration Resistant Prostate Cancer Patients Metastatic to Bone. | • Radiological progression-free survival                                           | • Overall survival                                                                   | 560                  | Recruiting    |
|            |            |                                                                     |                                                                                  | • prostate cancer specific survival                                                 |                      |               |
|            |            |                                                                     |                                                                                  | • First symptomatic skeletal event                                                   |                      |               |
|            |            |                                                                     |                                                                                  | • Time and incidence of first skeletal progression-free                              |                      |               |
|            |            |                                                                     |                                                                                  | • (…)                                                                              |                      |               |
| NCT02730338 | Phase 3    | INTense Exercise foR surVivAL Among Men With Metastatic Prostate Cancer (INTerval – GAPA4): a multicentre, randomised, controlled phase III. | • Overall Survival                                                                | • Disease progression                                                                | 866                  | Recruiting    |
|            |            |                                                                     |                                                                                  | • Symptomatic Skeletal Related Events                                               |                      |               |
|            |            |                                                                     |                                                                                  | • Analgesic/Opiate Use                                                              |                      |               |
|            |            |                                                                     |                                                                                  | • (…)                                                                              |                      |               |
groundwork for the use of enzalutamide in patients with mHSPC. This last study reported an increase in 3-year OS (80% vs. 72%; HR: 0.39; p < 0.001) and rPFS (p = 0.005) in favor of enzalutamide. In fact, in the ENZAMET study, the use of bone-directed therapies was used as a stratification factor (9.8% of patients). In the subgroup analysis, no clear clinical benefit was observed for OS (HR: 1.77; 95% confidence interval (CI) 0.83–3.77; p = 0.006) [66].

Similarly, the TITAN trial reported a benefit in the apalutamide group compared to placebo, both in OS (82.4% vs. 73.5%; HR: 0.67; 95% CI 0.51–0.89; p = 0.005) and rPFS (68.2% vs. 47.5%; HR: 0.48; 95% CI 0.39–0.60; p < 0.001), although no significant differences in time to first SRE were observed [67]. At present, there are no randomized prospective studies on the sequence of hormonal therapies that can allow us to define the optimal timing for these types of treatments or their combination with bone-directed therapies. Additional studies are needed to solve an issue that is appearing more and more frequently in the management of these patients.

5. Dose, scheme and treatment duration of bone-protecting agents for the prevention of skeletal-related events

Regarding the optimal administration of BPA, several trials compare dose escalation of both denosumab and ZA [69]. The results of a multicenter study that included patients with bone metastases from breast cancer and CRPC have recently been published. Of the 263 participants, 39.2% had mCRPC. The administration of 4 mg of iv ZA or 120 mg of subcutaneous denosumab every 12 weeks was not inferior to the monthly scheme in terms of quality of life. These results are consistent with previously published data. While we wait for the results of the REDUSE trial [70], de-escalating the dose of denosumab and ZA seems like a reasonable clinical decision based on the available evidence [71]. It must be noted that the most recent ESMO recommendations, while they also suggest de-escalation of ZA, still recommend the monthly denosumab. However, this last update was issued prior to the publication of this trial [28].

The optimal treatment duration of BPA for the prevention of SRES in patients with metastatic PCa is not well established. In the 2019 Advanced Prostate Cancer Consensus Conference, 61% of panelists agreed on maintaining therapy for 24 months in patients with mCRPC, 4% suggested treatment for five years and 31% opted for indefinite treatment [14]. The American Society of Clinical Oncology (ASCO) conducted a review of recommendations for bone health in patients with PCa. Relative to treatment duration with ZA or denosumab, they established that, although pivotal studies set a maximum of 24 months, the optimal duration to prevent SREs in mCRPC is not well defined [60] and further trials with longer follow-up are needed to gather more information on this topic.

6. Novel therapies

Recent studies focus on the identification of new therapies that may break the vicious cycle of bone metastasis by targeting osteoclasts. These include: endoteline antagonists (e.g., zibotentan), c-Scr inhibitors (e.g., dasatanib) and tirosin-kinase inhibitors (e.g., cabozantinib) [72–74]. However, despite their activity in other tumors, they haven’t managed to show significant results for PCa in phase III randomized trials.

7. Future directions

The survival improvement in patients with PCa is linked to the increase in the number of available treatments and the magnitude of the benefit of these therapies, which can have a cumulative impact in bone health over the years. Nowadays, most ongoing studies on the usefulness of new drugs in PCa include rPFS or time to first SRE as secondary endpoints (NCT03732820) (Table 2).

The assessment of bone health and the optimization of treatments to avoid its deterioration is key to elude the morbidity and mortality associated with the cancer-related loss of BMD. Non-pharmacological interventions such as lifestyle changes and physical activity are important to prevent SREs associated with ADT. For this reason, multiple ongoing clinical trials are evaluating the benefit that these changes in lifestyle could have in the oncologic patient (NCT04050397, NCT04507698).

After the 2019 Advanced Prostate Cancer Consensus Conference, there is still no agreement on the duration and treatment scheme with osteoclast-directed therapies in patients with mCRPC. Based on previously published results [71], phase III and IV studies are investigating de-escalation in the treatment frequency of denosumab from four weeks to 12 with the aim of determining possible differences quality of life and SREs in these patients (NCT04549207, NCT02051218).

In patients with CRPC, both second generation hormonal treatments and osteoclast-directed therapies have shown promising results in terms of prevention of metastases or SREs. However, the benefit of the combination of these two types of treatment is still uncertain given the low recruitment of the available clinical trials (NCT03869762). Therefore, there is still a need for further prospective studies that evaluate the synergies of both drugs.

8. Conclusions

The comprehensive management of advanced PCa must include an early evaluation of bone health. We need to carefully evaluate these patients in order to prevent a high proportion of patients experiencing SREs and subsequent deterioration in quality of life.

Next generation anti-androgens have improved the prognosis of patients with PCa, and together with BPA, delay the onset of SREs and radiological progression in dif-
frent scenarios of the disease. In addition to antiresorptive therapies, lifestyle changes and physical exercise seem to benefit these patients.

We must wait for the results of ongoing clinical trials that aim to demonstrate the clinical benefit of the concomitant treatment with BPA and next generation anti-androgens in non metastatic castration resistant prostate cancer patients.

Author contributions

MAGA, FLC, LPM, DB, JP, XM and JZ—preparation of the manuscript; FLC, FC and MAGA—coordination and final review of the manuscript; ACT, RB, PS and PO—final review of the manuscript.

Ethics approval and consent to participate

Not applicable.

Acknowledgment

AT acknowledges support from Cancer Research UK (C33589/A28284 and C7724A/28724) and the National Institute for Health Research (NIHR) Cancer Research Network. This project represents independent research supported by the National Institute for Health Research (NIHR) Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and the Institute of Cancer Research, London. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest.

References

[1] Meng MV, Grossfeld GD, Sadetsky N, Mehta SS, Lubeck DP, Carroll PR. Contemporary patterns of androgen deprivation therapy use for newly diagnosed prostate cancer. Urology. 2002; 60: 7–11.
[2] Saad F, Adachi JD, Brown JP, Canning LA, Gelmon KA, Josse RG, et al. Cancer Treatment–Induced Bone Loss in Breast and Prostate Cancer. Journal of Clinical Oncology. 2008; 26: 5465–5476.
[3] Al-Shamsi HO, Lau AN, Malik K, Alamri A, Ioannidis G, Corbett T, et al. The Current Practice of Screening, Prevention, and Treatment of Androgen-Deprivation-Therapy Induced Osteoporosis in Patients with Prostate Cancer. Journal of Oncology. 2012; 2012: 1–7.
[4] Rosino Sanchez A. Manejo preventivo de la enfermedad ósea en cáncer de próstata avanzado. Archivos Españoles de Urología. 2018; 71: N: 258–266. (In Spanish)
[5] Walsh PC. Risk of fracture after androgen deprivation for prostate cancer. The Journal of Urology. 2005; 174: 929–930.
[6] Shahinian VB, Kuo Y, Freeman JL, Goodwin JS. Risk of Fracture after Androgen Deprivation for Prostate Cancer. New England Journal of Medicine. 2005; 352: 154–164.
[7] Oster G, Lamerato L, Glass AG, Richert-Boe KE, Lopez A, Chung K, et al. Natural history of skeletal-related events in patients with breast, lung, or prostate cancer and metastases to bone: a 15-year study in two large us health systems. Supportive Care in Cancer. 2013; 21: 3279–3286.
[8] Smith MR, Saad F, Oudard S, Shore N, Fizazi K, Sieber P, et al. Denosumab and Bone Metastasis–Free Survival in Men with Nonmetastatic Castration-Resistant Prostate Cancer: Exploratory Analyses by Baseline Prostate-Specific Antigen Doubling Time. Journal of Clinical Oncology. 2013; 31: 3800–3806.
[9] Smith MR, Egerdie B, Toriz NH, Feldman R, Tammela TLJ, Saad F, et al. Denosumab in Men Receiving Androgen-Deprivation Therapy for Prostate Cancer. New England Journal of Medicine. 2009; 361: 745–755.
[10] Fizazi K, Carducci M, Smith M, Damiao R, Brown J, Karsh L, et al. Denosumab versus zolendronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet. 2011; 377: 813–822.
[11] Morote J, Planas J. Pérdida de masa ósea en pacientes con cáncer de próstata sometidos a deprivación androgénica. Actas Urológicas Españolas. 2011; 35: 232–239. (In Spanish)
[12] Brawer MK. Hormonal therapy for prostate cancer. Reviews in Urology. 2006; 8: S35–S47.
[13] Morote J, Morin JP, Orsolà A, Abascal JM, Salvador C, Trilla E, et al. Prevalence of osteoporosis during long-term androgen deprivation therapy in patients with prostate cancer. Urology. 2007; 69: 500–504.
[14] Gillessen S, Attard G, Beer TM, Beltran H, Bjartell A, Bossi A, et al. Management of Patients with Advanced Prostate Cancer: Report of the Advanced Prostate Cancer Consensus Conference 2019. European Urology. 2020; 77: 508–547.
[15] Suominen MI, Fagerlund KM, Rissanen JP, Konkol YM, Morko JP, Peng Z, et al. Radium-223 Inhibits Osseous Prostate Cancer Growth by Dual Targeting of Cancer Cells and Bone Microenvironment in Mouse Models. Clinical Cancer Research. 2017; 23: 4335–4346.
[16] Auchus RJ, Yu MK, Nguyen S, Mundle SD. Use of Prednisone for Abriraterone Acetate in Metastatic Castration-Resistant Prostate Cancer. The Oncologist. 2014; 19: 1231–1240.
[17] Smith M, Parker C, Saad F, Miller K, Tombal B, Ng QS, et al. Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncology. 2019; 20: 408–419.
[18] Saad F, Shore N, Van Poppel H, Rathkopf DE, Smith MR, de Bono JS, et al. Impact of Bone-targeted Therapies in Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer Patients Treated with Abiraterone Acetate: Post Hoc Analysis of Study COU-AA-302. European Urology. 2015; 68: 570–577.
[19] James ND, Sydes MR, Clarke NW, Mason MD, Dearmaley DP, Spears MR, et al. Addition of docetaxel, zoledronic acid, or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomised, double-blind, placebo-controlled trial, phase 3 trial. Lancet. 2016; 387: 1163–1177.
[20] Sartor O, Coleman R, Nilsson S, Heinrich D, Helle SI, O’Sullivan JM, et al. Effect of radium-223 dichloride on symptomatic skeletal events in patients with castration-resistant prostate cancer and bone metastases: results from a phase 3, double-blind, randomised trial. The Lancet Oncology. 2014; 15: 738–746.
[21] Johnell O, Kanis JA, Odén A, Johansson H, De Laet C, Delmas P, et al. Predictive value of BMD for hip and other fractures. Journal of Bone and Mineral Research. 2005; 20: 1185–1194.
[22] Kanis JA, Cooper C, Rizzoli R, Reginster J-Y. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporosis International. 2019; 30: 3–44.

[23] Siris ES, Miller PD, Barrett-Conner E, Faulkner KG, Wehren LE, Abbott TA, et al. Identification and Fracture Outcomes of Undiagnosed Low Bone Mineral Density in Postmenopausal Women. Journal of the American Medical Association. 2001; 286: 2815.

[24] Compston J, Cooper A, Cooper C, Gittoes N, Gregson C, Harvey N, et al. UK clinical guideline for the prevention and treatment of osteoporosis. Arch Osteoporos. 2017; 12: 43.

[25] McCloskey EV, Harvey NC, Johansson H, Kanis JA. FRAX updates 2016. Current Opinion in Rheumatology. 2016; 28: 433–441.

[26] Briot K, Pacjou J, Beuzeboc P, Bonneterre J, Bouvard B, Confavreux CB, et al. French recommendations for osteoporosis prevention and treatment in patients with prostate cancer treated by androgen deprivation. Joint Bone Spine. 2019; 86: 21–28.

[27] EAU Guidelines. Edn. presented at the EAU Annual Congress Milan 2021. ISBN 978-94-92671-13-4.

[28] Coleman R, Hadij P, Body J-J, Santini D, Chow E, Terpos E, et al. Bone health in cancer: ESMO Clinical Practice Guidelines. Annals of Oncology. 2020; 31: 1650–1663.

[29] Hadij P, Aapro MS, Body J-J, Granti M, Brandi ML, Register JY, et al. Management of Aromatase Inhibitor-Associated Bone Loss (AIBL) in postmenopausal women with hormone sensitive breast cancer: Joint position statement of the IOF, CABS, ECTS, IEG, ESCEO, IMS, and SIOG. Journal of Bone Oncology. 2017; 7: 1–12.

[30] Saylor PJ, Kaufman DS, Michaelson MD, Lee RJ, Smith MR. Application of a Fracture Risk Algorithm to Men Treated with Androgen Deprivation Therapy for Prostate Cancer. Journal of Urology. 2010; 183: 2200–2205.

[31] Bressi B, Cagliari M, Contesini M, Mazzini E, Bergamaschi FAM, Moscato A, et al. Physical exercise for bone health in men with prostate cancer receiving androgen deprivation therapy: a systematic review. Supportive Care in Cancer. 2021; 29: 1811–1824.

[32] Network NCC. No Title [Internet]. Prostate cancer Version 1.2022. 2022. Available at: https://www.nccn.org/professionals /physician_gls/pdf/prostate.pdf (Accessed: 15 December 2021).

[33] Reyes-Garcia R, García-Martín A, Varsavsky M, Rozas-Moreno P, Cortés-Berdonces M, Luque-Fernández J, et al. Actualización de las recomendaciones para la evaluación y tratamiento de la osteoporosis asociada a enfermedades endocrinas y nutricionales. Grupo de trabajo de osteoporosis y metabolismo mineral de la SEEN. Endocrinología Y Nutrición. 2015; 62: e47–e56. (In Spanish)

[34] Aliabbai SMH, Mohamedali HZ, Gulumhusein H, Panju AH, Breunis H, Timilshina N, et al. Changes in bone mineral density in men starting androgen deprivation therapy and the protective role of vitamin D. Osteoporosis International. 2013; 24: 2571–2579.

[35] Formenti AM, Dalla Volta A, di Filippo L, Berruti A, Giustina A. Effects of Medical Treatment of Prostate Cancer on Bone Health. Trends in Endocrinology & Metabolism. 2021; 32: 135–158.

[36] Jakob T, Tesfamariam YM, Macherey S, Kuh K, Adams A, Mensf I, et al. Bisphosphonates or RANK-ligand-inhibitors for men with prostate cancer and bone metastases: a network meta-analysis. Cochrane Database of Systematic Reviews. 2020; 12: CD013020.

[37] Smith MR, Eastham J, Gleason DM, Shasha D, Tchekmedyian S, Zinner N. Randomized Controlled Trial of Zoledronic Acid to Prevent Bone Loss in Men Receiving Androgen Deprivation Therapy for Nonmetastatic Prostate Cancer. Journal of Urology. 2003; 169: 2008–2012.

[38] Ryan CW, Hsu D, Demers LM, Beer TM, Lacerna LY. Zoledronic Acid Initiated During the First Year of Androgen Deprivation Therapy Increases Bone Mineral Density in Patients With Prostate Cancer. Journal of Urology. 2006; 176: 972–978.

[39] Michaelson MD, Kaufman DS, Lee H, McGovern FJ, Kantoff PW, Fallon MA, et al. Randomized Controlled Trial of Annual Zoledronic Acid to Prevent Gonadotropin-Releasing Hormone Agonist–Induced Bone Loss in Men with Prostate Cancer. Journal of Clinical Oncology. 2007; 25: 1038–1042.

[40] Kachnic LA, Pugh SL, Tai P, Smith M, Gore E, Shah AB, et al. RTOG 0518: randomized phase III trial to evaluate zoledronic acid for prevention of osteoporosis and associated fractures in prostate cancer patients. Prostate Cancer and Prostatic Diseases. 2013; 16: 382–386.

[41] Hussain M, Fizazi K, Saad F, Rathenborg P, Shore N, Ferreira U, et al. Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer. New England Journal of Medicine. 2018; 378: 2465–2474.

[42] Smith MR, Saad F, Chowdhury S, Oudard S, Hadaschik BA, Graff JN, et al. Alpertumide Treatment and Metastasis-free Survival in Prostate Cancer. New England Journal of Medicine. 2018; 378: 1408–1418.

[43] Fizazi K, Shore N, Tammela TL, Ulys A, Vjaters E, Poljakov S, et al. Dolatumide in Nonmetastatic, Castration-Resistant Prostate Cancer. New England Journal of Medicine. 2019; 380: 1235–1246.

[44] Smith MR, Saad F, Coleman R, Shore N, Fizazi K, Tombal B, et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. Lancet. 2012; 37: 39–46.

[45] Wirth M, Tammela T, Cicalesse V, Gomez Veiga F, Delaere K, Miller K, et al. Prevention of Bone Metastases in Patients with High-risk Nonmetastatic Prostate Cancer Treated with Zoledronic Acid: Efficacy and Safety Results of the Zomecta European Study (ZEUS). European Urology. 2015; 67: 482–491.

[46] Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, et al. A Randomized, Placebo-Controlled Trial of Zoledronic Acid in Patients with Hormone-Refractory Metastatic Prostate Carcinoma. JNCI Journal of the National Cancer Institute. 2002; 94: 1458–1468.

[47] Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, et al. Long-Term Efficacy of Zoledronic Acid for the Prevention of Skeletal Complications in Patients with Metastatic Hormone-Refractory Prostate Cancer. JNCI Journal of the National Cancer Institute. 2004; 96: 879–882.

[48] Barghout V, Abetz L, Arbuckle R, Bosch V, Hui Y, Saad F. Effect of zoledronic acid (Z) on pain in prostate cancer patients with bone metastases based on performance status. Journal of Clinical Oncology. 2006; 24: 14544.

[49] Abetz L, Barghout V, Arbuckle R, Bosch V, Shirina N, Saad F. Impact of zoledronic acid (Z) on pain in prostate cancer patients with bone metastases in a randomised placebo-control trial. Journal of Clinical Oncology. 2006; 24: 4638–4638.

[50] Saad F, Eastham J. Zoledronic Acid Improves Clinical Outcomes when Administered before Onset of Bone Pain in Patients with Prostate Cancer. Urology. 2010; 76: 1175–1181.

[51] Saad F. New research findings on zoledronic acid: Survival, pain, and anti-tumour effects. Cancer Treatment Reviews. 2008; 34: 183–192.

[52] Pan Y, Jin H, Chen W, Yu Z, Ye T, Zheng Y, et al. Docetaxel with or without zoledronic acid for castration-resistant prostate cancer. International Urology and Nephrology. 2014; 46: 2319–2326.
I, et al. Clinical Outcomes and Survival Following Treatment of Metastatic Castrate-Refractory Prostate Cancer with Docetaxel alone or with Strontium-89, Zoledronic Acid, or both. JAMA Oncology. 2016; 2: 493.

[54] Lipton A, Fizazi K, Stopeck AT, Henry DH, Brown JE, Yardley DA, et al. Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials. European Journal of Cancer. 2012; 48: 3082–3092.

[55] Smith MR, Coleman RE, Klotz L, Pittman K, Milecki P, Ng S, et al. Denosumab for the prevention of skeletal complications in metastatic castration-resistant prostate cancer: comparison of skeletal-related events and symptomatic skeletal events. Annals of Oncology. 2015; 26: 368–374.

[56] Clemons M, Liu M, Stober C, Pond G, Jemaan Alzahrani M, Ong M, et al. Two-year results of a randomised trial comparing 4-versus 12-weekly bone-targeted agent use in patients with bone metastases from breast or castration-resistant prostate cancer. Journal of Bone Oncology. 2021; 30: 100388.

[57] Gilles sen S, Choudhury A, Rodriguez-Vida A, Nole F, Gallardo Diaz E, Rou megure TA, et al. Decreased fracture rate by mandating bone protecting agents in the EORTC 1333/PEACEIII trial combining Ra223 with enzalutamide versus enzalutamide alone: an updated safety analysis. Journal of Clinical Oncology. 2021; 39: 5002–5002.

[58] O’Sullivan JM, Carles J, Cathomas R, Gomez-Iturriaga A, Heinrich D, Kramer G, et al. Radium-223 within the Evolving Treatment Options for Metastatic Castration-resistant Prostate Cancer: Recommendations from a European Expert Working Group. European Urology Oncology. 2020; 3: 455–463.

[59] Parker C, Nilsson S, Heinrich D, Helle SI, O’Sullivan JM, Fossà SD, et al. Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer. New England Journal of Medicine. 2013; 369: 213–223.

[60] Saylor PJ, Rumble RB, Tagawa S, Eastham JA, Finelli A, Reddy PS, et al. Bone Health and Bone-Targeted Therapies for Prostate Cancer: ASCO Endorsement of a Cancer Care Ontario Guideline. Journal of Clinical Oncology. 2020; 3: 1736–1743.

[61] Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. The New England Journal of Medicine. 2014; 371: 424–433.

[62] Smith MR, Halabi S, Ryan CJ, Hussain A, Vogelzang N, Stardler W, et al. Randomized Controlled Trial of Early Zoledronic Acid in Men With Castration-Sensitive Prostate Cancer and Bone Metastases: Results of CALGB 90202 (Alliance). Journal of Clinical Oncology. 2014; 32: 1143–1150.

[63] Kamba T, Kamoto T, Maruo S, Kikuchi T, Shimizu Y, Namiki S, et al. A phase III multicenter, randomized, controlled study of combined androgen blockade with versus without zoledronic acid in prostate cancer patients with metastatic bone disease: results of the ZAPCA trial. International Journal of Clinical Oncology. 2017; 22: 166–173.

[64] Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, et al. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. The New England Journal of Medicine. 2017; 377: 352–360.

[65] James ND, de Bono JS, Spears MR, Clarke NW, Mason MD, Dearnaley DP, et al. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. New England Journal of Medicine. 2017; 377: 338–351.

[66] Davis ID, Martin AJ, Stockler MR, Begbie S, Chowdhury S, et al. Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. New England Journal of Medicine. 2019; 381: 121–131.

[67] Chi KN, Agarwal N, Bjartell A, Chung BH, Gomes AJP de S, Given R, et al. Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer. New England Journal of Medicine. 2019; 202: 661.

[68] Armstrong AJ, Szmulewitz RZ, Petrylak DP, Holzbeierlein J, Villers A, Azad A, et al. ARCHES: a Randomized, Phase III Study of Androgen Deprivation Therapy with Enzalutamide or Placebo in Men with Metastatic Hormone-Sensitive Prostate Cancer. Journal of Clinical Oncology. 2019; 37: 2974–2986.

[69] Liu C, Wang L, Liu L, Zhuang J, Tang S, Zhang T, et al. Efficacy and safety of de-escalation bone-modifying agents for cancer patients with bone metastases: a systematic review and meta-analysis. Cancer Management and Research. 2018; 10: 3809–3823.

[70] Templeton AJ, Stalder L, Albiges Sauvin L, Bernhard J, Brauschke P, Gilles sen S, et al. Prevention of Symptomatic Skeletal Events with Denosumab Administered every 4 Weeks Versus every 12 Weeks—a Non-Inferiority Phase III Trial: Sakk 96/12 - Reduse. Annals of Oncology. 2014; 25: iv540.

[71] Clemons M, Ong M, Stober C, Ernst S, Booth C, Canil C, et al. A randomised trial of 4-versus 12-weekly administration of bone-targeted agents in patients with bone metastases from breast or castration-resistant prostate cancer. European Journal of Cancer. 2021; 142: 132–140.

[72] Fizazi K, Higano CS, Nelson JB, Gleave M, Miller K, Morris T, et al. Phase III, Randomized, Placebo-Controlled Study of Docetaxel in Combination with Zibotentan in Patients with Metastatic Castration-Resistant Prostate Cancer. Journal of Clinical Oncology. 2013; 31: 1740–1747.

[73] Arajuo JC, Trudel GC, Saad F, Armstrong AJ, Yu EY, Bellmunt J, et al. Docetaxel and dasatinib or placebo in men with metastatic castration-resistant prostate cancer (READY): a randomised, double-blind phase 3 trial. The Lancet Oncology. 2013; 14: 1307–1316.

[74] Smith M, De Bono J, Sternberg C, Le Moulec S, Oudard S, De Giorgi U, et al. Phase III Study of Cabozantinib in Previously Treated Metastatic Castration-Resistant Prostate Cancer: COMET-I. Journal of Clinical Oncology. 2016; 34: 3005–3013.