



General and Supportive Care

Management of bone health in solid tumours: From bisphosphonates to a monoclonal antibody



Roger von Moos^{a,*}, Luis Costa^b, Eva Gonzalez-Suarez^c, Evangelos Terpos^d, Daniela Niepel^e, Jean-Jacques Body^f

^a Kantonsspital Graubünden, Loëstrasse 170, Chur, Graubünden, Switzerland

^b Hospital de Santa Maria, Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa, Avenida Professor Egas Moniz, Lisboa, Portugal

^c Cancer Epigenetics and Biology Program (PEBC), Bellvitge Biomedical Research Institute, (IDIBELL) Avinguda Gran Via de l'Hospitalet, Barcelona, Spain

^d Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece

^e Amgen (Europe) GmbH, Rotkreuz, Switzerland

^f Department of Medicine, CHU Brugmann, Université Libre de Bruxelles, Place A. Van Gehuchten 4, 1020 Brussels, Belgium

ARTICLE INFO

Keywords:

Bisphosphonates

Bone metastases

Cancer treatment-induced bone loss

Denosumab

Skeletal-related events

ABSTRACT

Patients with solid tumours are at risk of impaired bone health from metastases and cancer therapy-induced bone loss (CTIBL). We review medical management of bone health in patients with solid tumours over the past 30 years, from first-generation bisphosphonates to the receptor activator of nuclear factor κ B ligand (RANKL)-targeted monoclonal antibody, denosumab. In the 1980s, first-generation bisphosphonates were shown to reduce the incidence of skeletal-related events (SREs) in patients with breast cancer. Subsequently, more potent second- and third-generation bisphosphonates were developed, particularly zoledronic acid (ZA). Head-to-head studies showed that ZA was significantly more effective than pamidronate for reducing SREs in patients with breast and castrate-resistant prostate cancer (CRPC), becoming the standard of care for more than a decade. The RANKL inhibitor denosumab was licensed in 2010, and head-to-head studies and integrated analyses confirmed its superiority to ZA for preventing SREs, particularly in breast cancer and CRPC. Bisphosphonates and denosumab have also been investigated for prevention of CTIBL in patients receiving hormonal therapy for breast and prostate cancer, and denosumab is licensed in this indication. Despite advances in management of bone health, several issues remain, notably the optimal time to initiate therapy, duration of therapy, and dosing frequency, and how to avoid toxicity, particularly with long-term treatment. In summary, introduction of ZA and denosumab has protected patients with bone metastasis from serious bone complications and improved their quality of life. Ongoing research will hopefully guide the optimal use of these agents to help maintain bone health in patients with solid tumours.

Introduction

Bone health is an important consideration in patients with solid tumours, as both metastasis to bone and cancer therapy-induced bone loss (CTIBL) can increase morbidity and reduce quality of life [1,2]. Bone is a common site of metastasis in patients with cancer, with prostate, breast and lung the most frequent tumours leading to bone metastasis, accounting for 34%, 22% and 20% of cases, respectively [3]. A recent study in patients with solid tumours in the USA estimated the incidence of bone metastases in patients with solid tumours to be 6.9% at 5 years after diagnosis and 8.4% at 10 years [4], while a meta-analysis of 156 studies in breast cancer found that a median of 12% of patients with stage I–III breast cancer developed bone metastases

during a median follow-up period of 60 months [5]. The incidence of bone metastasis is, however, difficult to estimate, with most studies generally based on clinical records and autopsy data, and so may not reflect current treatment patterns [4]. The true incidence of bone metastasis is, therefore, unknown [2]. Metastasis begins when cancer cells escape from the primary tumour and enter the circulation [1,2,6]. These circulating cancer cells have affinities for specific tissue types, such as bone – this is known as the ‘seed and soil’ hypothesis. When circulating cancer cells infiltrate bone, a vicious cycle is triggered in which signalling between cancer cells and bone cells leads to the development of the metastatic lesion [1,6]. Bone metastases can be broadly classified as osteoclastic, characterised primarily by destruction of normal bone, and osteoblastic, characterised by deposition of new

* Corresponding author at: Kantonsspital Graubünden, Loëstrasse 170, CH-7000 Chur, Switzerland.

E-mail address: roger.vonmoos@ksgr.ch (R. von Moos).

<https://doi.org/10.1016/j.ctrv.2019.05.003>

Received 13 December 2018; Received in revised form 23 April 2019; Accepted 13 May 2019

0305-7372/ © 2019 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

bone [2].

Bone metastases are a major cause of morbidity, including skeletal-related events (SREs, usually defined as fracture, spinal cord compression, need for radiation therapy or surgery, and less often tumour-related hypercalcaemia, although exact definitions can vary between clinical trials), severe pain, impaired mobility, and bone marrow aplasia [2]. Pathologic fractures occur in 10–30% of all cancer patients, with higher rates in some cancers such as multiple myeloma (up to 37%) and breast cancer (up to 52%) [7,8]. Such fractures occur most frequently in the ribs and vertebrae. As a result, bone metastases have a substantial impact on patients' quality of life and contribute to increased healthcare costs [1,2,6,9–11].

The treatment of bone metastases in patients with solid tumours is generally palliative, with very limited opportunities for complete eradication [12]. Bone metastases can be managed with a range of therapeutic modalities, including external beam radiotherapy, endocrine treatments, chemotherapy and radioisotopes, as well as orthopaedic intervention to correct structural complications or nerve compression. These treatments are accompanied by further medical care to prevent fractures and other bone complications using various bisphosphonates and the receptor activator of nuclear factor κ B ligand (RANKL)-targeted agent denosumab, which are licensed for the prevention of SREs in patients with bone metastases due to solid tumours (Supplementary Table 1; Fig. 1) [13–48].

In the early 21st century, the potential of bisphosphonates and denosumab was recognised for the management of CTIBL, another bone-related complication experienced by some patients with cancer [49,50]. Oestrogen and testosterone have both direct and indirect effects on bone metabolism, and the reduced levels of these hormones resulting from hormone ablation therapy in patients with breast and prostate cancer may lead to loss of bone mass and an increased risk of osteoporotic fractures. Men receiving androgen deprivation therapy for prostate cancer may also undergo loss of muscle mass, with resulting indirect effects on bone [49].

The aim of this review is to provide a historical perspective on the medical management and consequences of bone metastases and CTIBL, using the available data to encourage best practice and to highlight the benefits of early and sustained treatment.

History of the management of bone metastasis complications

Management of the consequences of bone metastases with bisphosphonates began in the 1980s with the development of the first-

generation intravenous bisphosphonate clodronate, which was licensed in Europe in 1992 for management of osteolytic lesions, hypercalcaemia and bone pain associated with skeletal metastases in patients with carcinoma of the breast or multiple myeloma (Supplementary Table 1). This was followed by the second- and third-generation agents, most notably zoledronic acid (ZA), which was first approved in 2001. Bisphosphonates are chemically stable analogues of pyrophosphate compounds such as inorganic pyrophosphate, which are found widely in nature [51]. The high affinity of bisphosphonates for calcium ions means that they attach to hydroxyapatite binding sites on the bone surface, especially in locations undergoing active resorption. The bisphosphonate molecule is then internalised by osteoclasts during resorption, leading to inhibition of osteoclast function [6]. With first-generation, non-nitrogen-containing bisphosphonates, this process occurs via the disruption of cellular metabolism, leading ultimately to apoptosis [1].

The second- and third-generation bisphosphonates differ from first-generation agents because they have a nitrogen-containing side group. These agents can be divided into alkyl-amino bisphosphonates (the second-generation agents pamidronate, alendronate, risedronate, and the third-generation agent ibandronate) and heterocyclic bisphosphonates (the third-generation agent ZA; see below). The nitrogen-containing bisphosphonates are generally more potent than first-generation agents as, in addition to hydroxyapatite binding, they impair intracellular signalling in osteoclasts by inhibiting the enzyme farnesyl diphosphate synthase [1,51]. The third-generation bisphosphonates differ from second-generation agents in that the nitrogen group is contained in the R2 side-chain, leading to more potent inhibition of farnesyl synthase, a key enzyme in metabolic pathways involved in osteoclast morphology and function [52].

In 2010, the first, and to date only, RANKL-targeted monoclonal antibody, denosumab, was also licensed for management of the consequences of bone metastases from solid tumours. Management of bone metastases is generally evaluated in terms of the prevention of SREs, using parameters such as time to first SRE, skeletal morbidity rate or multiple-event analysis [12,53]. Other endpoints used to evaluate efficacy relevant from the patient's perspective include bone pain (evaluated as an adverse event or using instruments such as the Bone Pain Index), and survival.

First-generation bisphosphonates

Bisphosphonates were first used successfully in patients with cancer

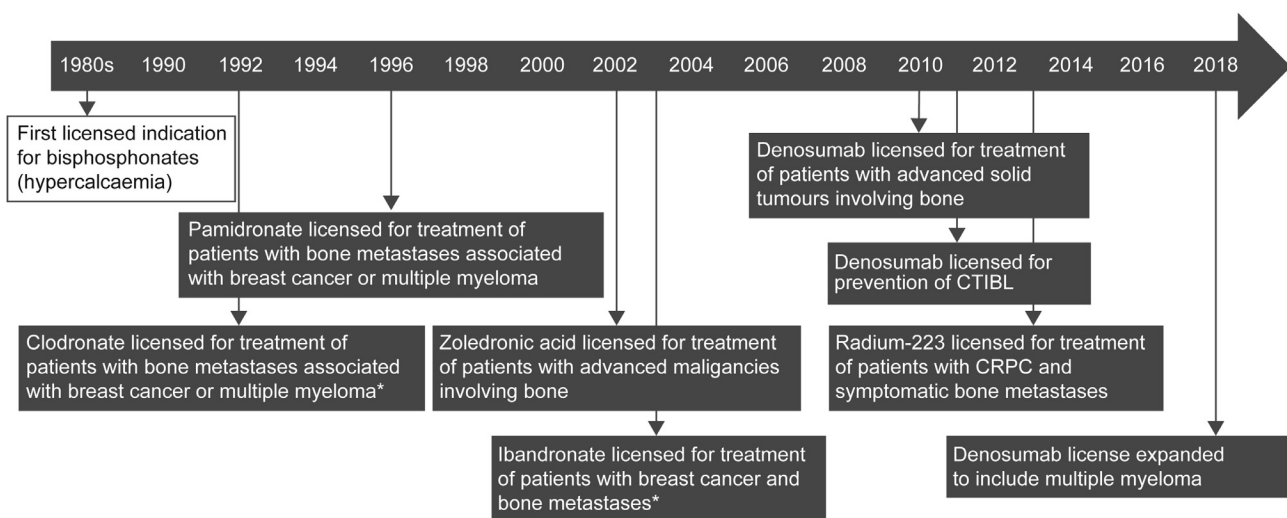


Fig. 1. Timeline of key events in the development of bisphosphonates and denosumab in the management of bone health in patients with advanced malignancies. * Not licensed in the USA. CRPC = castrate-resistant prostate cancer; CTIBL = cancer therapy-induced bone loss.

Table 1

Key results from studies of bisphosphonates and denosumab in patients with solid tumours and bone metastases.

Study	Year	Duration	Treatment	SRE, %	Time to first SRE, days	SMR, events per year
<i>Breast cancer</i>						
Hortobagyi et al. [28]	1996	12 cycles	Pamidronate	43 [*]	399 ^{*†}	–
			Placebo	56	213 [†]	
Theriault et al. [29]	1999	24 cycles	Pamidronate	56 [*]	317 ^{*†}	2.4 [*]
			Placebo	67	210 [†]	3.8
Rosen et al. [30] [‡]	2001	13 months	ZA	44	373	1.13
			Pamidronate	46	363	1.40
Berenson et al. [32]	2001	10 months	ZA	33	231	–
			Pamidronate	30	254	
Rosen et al. [31] [‡]	2003	25 months	ZA	47	376	1.04
			Pamidronate	51	356	1.33
Body et al. [39]	2003	96 weeks	IV ibandronate	51 [*]	354 [*]	–
			Placebo	62	232	
Rosen et al. [33]	2004	12 months	ZA	43	310 [*]	0.98
			Pamidronate	45	174	1.55
Body et al. [40]	2004	96 weeks	Oral ibandronate	45	632	–
			Placebo	52	454	
Stopeck [41]	2010	34 months [#]	Denosumab	–	NR	0.45
			ZA	–	804 [†]	0.58
Barrett-Lee et al. [34]	2014	96 weeks	ZA	41	693	0.44
			Oral ibandronate	42	679	0.50
<i>Castrate-resistant prostate cancer</i>						
Saad et al. [35]	2002	15 months	ZA	33 [*]	NR [*]	0.80
			Placebo	44	321	1.49 [†]
Saad et al. [36]	2004	24 months	ZA	38 [*]	488 [*]	0.77 [*]
			Placebo	49	321	1.47
Fizazi et al. [42]	2011	11–12 months [#]	Denosumab	36	630 ^{*†}	–
			ZA	41	520 [†]	
<i>Solid tumours</i>						
Rosen et al. [37]	2003	9 months	ZA	38	230 [*]	2.24
			Placebo	44	163	2.52
Rosen et al. [38]	2004	21 months	ZA	39	236 [*]	1.74 [†]
			Placebo	46	155	2.71
Henry et al. [43] [‡]	2011	7 months [#]	Denosumab	–	627 [†]	–
			ZA	–	496 [†]	
Henry et al. [44]	2014	6–7 months [#]	Denosumab	–	651 ^{*†}	–
			ZA	–	469 [†]	

Abbreviations: IV = intravenous; NR = not reached; SMR = skeletal morbidity rate; SRE = skeletal-related event; ZA = zoledronic acid.

^{*} p < 0.05 vs comparator.[†] Converted from months using the formula Days = Months × 30.4375.[‡] Also includes patients with multiple myeloma.[#] Median duration.

for the treatment of hypercalcaemia in the early 1980s, many years before data from large randomised, controlled trials showed they could prevent SREs [51]. Hypercalcaemia of malignancy was the setting used to derive active bisphosphonate doses for the treatment of bone metastases. Small placebo-controlled studies of clodronate in women with breast cancer metastatic to the bone began in the 1980s [54]. These studies showed benefit in terms of bone pain, extension of bone metastases into soft tissue and formation of new osteolytic foci, but approval by regulatory agencies did not occur until these data were confirmed in larger randomised controlled trials [24]. In metastatic castration-resistant prostate cancer (CRPC), the efficacy of clodronate is limited, with no beneficial effect on SREs (Table 1) [25–27], and treatment is not licensed in these patients.

Second-generation bisphosphonates

The clinical activity of nitrogen-containing bisphosphonates was first demonstrated in studies of pamidronate by a number of European groups in the early 1990s [55–57]. The first randomised, placebo-controlled trials were conducted in the USA in the mid-to-late 1990s, and results showed that pamidronate reduced skeletal morbidity by ~33%, increased median time to SRE by ~50%, and reduced the proportion of patients who experienced SREs by ~20% [28,29]. It is important to note, however, that the therapeutic anticancer landscape

has changed considerably over the past 20 years, and so these values must be interpreted in context and may no longer be valid with respect to current standard of care.

By the late 1990s, the potential of bisphosphonates in the treatment of patients with bone metastases had been confirmed [58–60]. In 1996, pamidronate was approved for the treatment of complications arising from osteolytic metastases in breast cancer, and soon became the treatment of choice [30,61]. While other second-generation bisphosphonates, including alendronate, are available for the treatment of osteoporosis, they are not licensed for the management of bone metastasis complications.

Bisphosphonate treatment is generally well tolerated, the main side effects being acute-phase reactions (e.g. chills, fever, bone pain and fatigue) and changes in serum ion levels, particularly calcium, magnesium and phosphorus [62]. Bisphosphonates are also associated with a dose- and infusion-rate-dependent impact on renal function, and renal function should be monitored during treatment [62]. In some patients receiving long-term bisphosphonate therapy, particularly with nitrogen-containing bisphosphonates, osteonecrosis of the jaw (ONJ) has been reported as a result of effects on osteoclast-mediated bone resorption and osteoclast formation [63].

Third-generation bisphosphonates

The third-generation bisphosphonate ZA differs from other bisphosphonates in that the nitrogen-containing R2 side-chain is a heterocyclic ring [64]. In addition to having increased potency on bone, ZA is also administered in a 15-min infusion, compared with 2 h for pamidronate. Furthermore, data suggest that ZA has anti-neoplastic effects resulting from decreased dissemination of tumour cells in bone marrow, inhibition of tumour cell adhesion, invasion, and proliferation, induction of apoptosis and inhibition of angiogenesis [64–68]. The clinical relevance of these effects has not been established.

In 1999, the first data demonstrating the clinical activity of ZA (in patients with cancer-related hypercalcaemia) were published [69]. Subsequently, several placebo-controlled and head-to-head studies of ZA versus other bisphosphonates were conducted in patients with metastatic breast cancer [30–34] and CRPC [35,36]. ZA was found to be more effective than pamidronate for reducing the incidence of SREs (primary endpoint in most studies), although this difference was not statistically significant in all studies (Table 1). One study in breast cancer also demonstrated a significant increase in time to first SRE (secondary endpoint) with ZA versus pamidronate [33]. The incidence of bone pain was similar with these agents [30,31,33].

ZA is the only bisphosphonate shown to significantly reduce skeletal complications from bone metastases in men with advanced prostate cancer [12], but the benefits of ZA are less clear in men with hormone-sensitive prostate cancer (HSPC) and bone metastases. Data from a randomised, controlled trial showed no difference in overall survival between ZA and placebo, and only a small numerical benefit for ZA in terms of the time to first SRE [70]. Information about the efficacy of ZA in other solid tumours is sparse. Most data come from a single randomised, double-blind, placebo-controlled trial in patients with mixed solid tumours, including lung cancer [37]. Overall, ZA was associated with a slight reduction in the incidence of SREs (primary endpoint) after 9 months versus placebo, a significantly prolonged time to first SRE and a reduced annual incidence of SREs. In the longer term (21 months), ZA significantly reduced the percentage of patients who experienced SREs and prolonged the time to first SRE compared with placebo (Table 1) [38]. Furthermore, in a retrospective analysis of data from the study, ZA was associated with reduced mortality versus placebo in the subset of patients who had elevated levels of the bone turnover marker N-telopeptide of type I collagen [71]. This positive effect on survival in patients with poor prognostic features, including elevated levels of bone markers, was confirmed in a subsequent exploratory analysis of three randomised controlled trials of ZA in patients with solid tumours [72]. ZA has also been the treatment of choice for myeloma-related bone disease [73], further discussion of which is outside the scope of the current paper.

Nephrotoxicity is one of the most clinically significant adverse events associated with ZA. It can limit ZA use in patients receiving chemotherapy agents such as cisplatin, particularly in patients who are older, with comorbidities and, in the case of lung cancer, a history of tobacco use [53]. Other notable side effects with ZA are similar to those of the first- and second-generation bisphosphonates, including acute-phase reactions, hypocalcaemia, and ONJ [53]. In an attempt to reduce the increased risk of ONJ resulting from accumulation of ZA in bone with prolonged administration, extended dosing intervals (every 12 weeks vs the standard dosing interval of 4 weeks) have been investigated [74–76]. Results to date suggest that dosing every 12 weeks is non-inferior to dosing every 4 weeks in terms of prevention of SREs; this may be related to the preferential binding, potency and accumulation of ZA in bone, prolonging its pharmacologic activity. The incidence of ONJ was similar or lower with dosing every 12 weeks compared with dosing every 4 weeks [74–76]. In the largest study, however, significantly more patients receiving ZA every 12 weeks required bone surgery within 2 years of enrolment (secondary endpoint) compared with 4-weekly ZA (4.8% vs 2.5%, respectively) [76]. It

should be noted, however, that this was an open-label non-inferiority study in which a high percentage of patients (40%) withdrew before experiencing an SRE, and there was no assessment of survival. Thus, overall data from studies of extended-interval ZA dosing to date support the use of 12-weekly treatment. It is not clear, however, whether there are subgroups, such as those with aggressive bone disease, who would benefit more from 4-weekly treatment or in whom 12-weekly treatment should be introduced after a period (e.g. 1 year) of monthly treatment.

Ibandronate is a third-generation bisphosphonate approved in Europe since 2003 as oral and intravenous formulations for prevention of SREs in patients with breast cancer. In randomised, placebo-controlled trials, oral and intravenous ibandronate were both found to reduce the incidence of new bone events by 38% [39,40]. While ibandronate has been shown to have similar effects on serum cross-linked C-terminal telopeptide of type I collagen (CTX), urinary CTX, bone alkaline phosphatase, amino-terminal procollagen propeptide of type I collagen, and osteocalcin as ZA in a Phase III study [77], a second Phase III study showed that oral ibandronate was inferior to ZA in terms of preventing SREs [34]. Oral ibandronate may, however, be an alternative agent for patients who have a strong preference for oral treatment or in whom convenience of treatment is an important factor [34,78]. The third-generation bisphosphonate risedronate is licensed for the treatment of osteoporosis in Europe and the USA, and Paget's disease in the USA, but has not been approved for the management of complications arising from bone metastases.

Overall, data show that ZA is the most active bisphosphonate in terms of preventing morbidity from bone metastases in patients with breast cancer, CRPC, lung and other solid tumours [53,79]. From its first approval in 2002 [80], ZA became standard of care for the prevention of skeletal complications in patients with bone metastases from solid tumours for more than a decade [81]. In the mid-2000s, it was noted, however, that SREs still occurred in patients receiving ZA and metastases continue to progress in the skeleton [82].

RANKL-targeted monoclonal antibodies: Denosumab

One of the key regulatory factors in bone remodelling is RANKL [83]. RANKL mediates osteoclast formation, function and survival, and is an important therapeutic target in the management of bone metastases [84], as the receptor RANK is expressed in a range of tumour types, including breast and lung cancers [81,85–88]. Denosumab is a human monoclonal IgG2 antibody that acts by binding with high affinity to membrane-bound and soluble forms of RANKL, decreasing osteoclast formation and activity [1,83,84]. Denosumab may also have effects on tumour cells independent of its role in bone homeostasis [81,89]. For example, the pro-tumourigenic effects of progesterone are mediated largely via RANKL [87,90–92], while RANK signalling induces stem-cell characteristics in human and mouse mammary epithelial cells, increasing recurrence and metastasis [88,93,94]. These effects have been observed primarily in preclinical studies, and their clinical relevance is unknown, although a similar effect of RANKL as a mediator of progesterone has also been observed in female mammary epithelia from patients undergoing mastoplasties and in carriers of the *BRCA1* gene [91,95]. This suggests a possible role for RANKL inhibitors in the prevention of breast cancer in women at high risk.

Data from an early study utilising single denosumab doses of 0.1, 0.3, 1.0, or 3.0 mg/kg demonstrated rapid suppression of bone turnover in patients with bone metastases, as well as greater reductions in bone turnover markers than with a single 90 mg dose of pamidronate [96]. Numerous head-to-head studies of denosumab (120 mg every 4 weeks) versus ZA (4 mg every 4 weeks) have been conducted in patients with different tumour types, including breast cancer [41], prostate cancer [42] and other solid tumours [43–45]. These pivotal studies were non-inferiority trials, designed to allow superiority testing according to the Hochberg method as a secondary endpoint and acknowledged by the US Food and Drug Administration. In addition, pooled analyses have been

Table 2

Key results from an integrated analysis of three head-to-head studies (n = 5723) comparing denosumab and zoledronic acid [99].

Parameter	Hazard ratio (95% CI) ^a	P-value
Time to first SRE (primary endpoint)	0.83 (0.76–0.90)	< 0.001
Time to multiple SREs	0.83 (0.76–0.90)	< 0.001
Pain worsening	0.92 (0.86–0.99)	0.026
Overall survival	0.98 (0.91–1.06)	0.617
Disease progression	1.02 (0.96–1.09)	0.697

Abbreviations: CI = confidence interval; SRE = skeletal-related event.

^a Values < 1 favour denosumab.

conducted of three studies in breast cancer, prostate cancer, other solid tumours and multiple myeloma (for which denosumab was recently licensed; Fig. 1) [97,98]. In an integrated analysis of head-to-head studies (n = 5723), denosumab significantly delayed the time to first SRE compared with ZA in patients with solid tumours and bone metastases (Table 2) [99]. Denosumab also delayed time to multiple SREs and pain worsening, while the drugs had a similar effect on overall survival and disease progression (Table 2). In the lung cancer subgroup of a study in patients with solid tumours, however, denosumab was associated with improved overall survival compared with ZA [45]. To date there are no Phase III data to demonstrate that denosumab treatment can prevent SREs in patients with metastatic HSPC [49], although such tumours are covered by the product label [20,21].

Unlike many bisphosphonates, which are administered intravenously, denosumab is given subcutaneously as a single 120-mg injection every 4 weeks, improving the convenience and acceptability of treatment for patients [49,53,100], as well as the time required from healthcare professionals to deliver the medication [101]. The safety profile of denosumab is broadly similar to that of ZA, with both drugs associated with a low incidence of hypocalcaemia and ONJ. However, the incidences of hypocalcaemia and serious hypocalcaemia are higher with denosumab [102], as potent inhibition of osteoclast function reduces the amount of skeletal calcium released into the circulation, while the incidence of renal toxicity is higher with ZA [53]. Recent data show that the incidence of hypocalcaemia in patients receiving denosumab can be as high as 30% despite mandatory Vitamin D and calcium substitution, although Grade 3 + hypocalcaemia was rare (1.3%) [103]. Unlike ZA, however, denosumab is not cleared by the kidneys [104]. The incidence of hypocalcaemia is increased in patients with severe renal impairment receiving denosumab compared with patients with milder or no renal impairment. Other risk factors for hypocalcaemia include prostate cancer or small-cell lung cancer, reduced creatinine clearance, and higher baseline levels of the bone turnover markers urinary N-telopeptide of type I collagen and bone-specific alkaline phosphatase [105]. Recent data have shown, however, that the appearance of hypocalcaemia is very rare after 12 months of treatment [103].

Overall, denosumab has benefits over ZA in metastatic solid tumours because of its superior efficacy in terms of delaying the time to SREs, the convenience of a subcutaneous injection and the lack of requirement for renal monitoring [53,79]. These aspects are also important to patients in determining their preference for one treatment over another. When 484 European patients were asked what aspects of treatment were most important to them, delaying the time until first SRE and worsening pain, and a low risk of renal complications, were considered most important [100]. No significant difference in ONJ rates between denosumab and ZA has been reported in randomised controlled clinical trials [53,79]. However, in a registry study of ONJ in 327 adults with a diagnosis of any cancer and ONJ, 97% had previously received either bisphosphonates (56%), denosumab (18%), or both (21%) [106]. Whichever agent is prescribed, the risks of ONJ must be discussed with patients before beginning denosumab or bisphosphonate treatment. Dentists have a key role to play as part of the

multidisciplinary team in preventing and managing ONJ [107]. Maintaining dental hygiene, avoiding bone trauma, and preventing and treating dental infections before and during therapy are essential to minimise the risk of ONJ [108]. Furthermore, any necessary dental surgery should be completed before initiating therapy. If invasive dental surgery is required while patients are receiving bisphosphonate or denosumab therapy, it is recommended that treatment is withheld for 2 months after surgery, although there is little evidence in this area [108].

The potential health economic benefits of treatment must also be taken into account, as studies have shown that patients with solid tumours who experience ≥ 1 SRE incur additional healthcare-related costs [109,110]. Treatments that reduce the incidence of SREs, therefore, have the potential to reduce the cost burden to healthcare services and society. While the acquisition cost of the monoclonal antibody denosumab is higher than that of generic bisphosphonates, cost-effectiveness analysis has shown that incremental costs per quality-adjusted life year (QALY) and per SRE avoided with denosumab are well below willingness-to-pay thresholds, and thus denosumab can be considered cost effective for prevention of SREs [111,112]. In an alternative cost-effectiveness analysis conducted based on US data, denosumab and ZA were associated with similar QALYs gained, and thus the authors concluded that the lower cost of ZA made it the optimal treatment [113]. Other authors have, however, described significant methodological flaws in the analysis, including failing to account for the superiority of denosumab over ZA in terms of SRE reduction, underestimating the prevalence of SREs and their cost burden, and limiting the time horizon of the analysis to 2 years [114].

Bisphosphonates and denosumab for the prevention of CTIBL

In addition to their role in reducing the risk of SREs in patients with bone metastases, benefits were also reported for several nitrogen-containing bisphosphonates in preventing CTIBL in patients with breast and prostate cancer. Observed benefits include improved bone mineral density (BMD) with risedronate (lumbar spine, +2.2% vs –1.8% with placebo; hip, +1.8% vs –1.1% with placebo; both $P < .0001$) [115] and ibandronate (lumbar spine, +3.0% vs –3.2% with placebo; hip, +0.6% vs –3.9% with placebo; both $P < .001$) [116] in women with breast cancer receiving hormonal therapy. Furthermore, alendronate, risedronate and pamidronate prevented BMD loss in men with locally advanced prostate cancer [117]. Similarly, several ZA studies confirmed the benefits of treatment (4 mg every 6 months) for reducing aromatase inhibitor-related bone loss in women with breast cancer [118–122]. Findings showed that adverse events with bisphosphonate therapy were mild and could be either prevented with suitable measures or easily managed [68].

Compared with breast cancer, data relating to the use of ZA for the prevention of CTIBL in patients with prostate cancer receiving androgen-deprivation therapy are limited. The available data suggest that ZA can improve BMD during androgen-deprivation therapy [123], although it is not clear whether this translates to improved fracture rates, and treatment is not associated with prolonged survival [124].

Denosumab has also been evaluated for the prevention of CTIBL in patients with breast cancer [125,126], HSPC [127] and CRPC [128,129]. For example, in the Austrian Breast & Colorectal Cancer Study Group-18 study, 3420 postmenopausal patients with early hormone receptor-positive breast cancer receiving treatment with aromatase inhibitors were randomised to denosumab 60 mg every 6 months or placebo [126]. The results of the primary analysis showed a significant reduction in the time to first fracture in women receiving denosumab compared with placebo, independently of baseline BMD (HR: 0.50; 95% CI: 0.39–0.65; $P < .0001$). Denosumab (as Prolia®, Amgen, Thousand Oaks, CA, USA) was licensed in 2011 for treatment of osteoporosis in postmenopausal women and for men at an increased risk of fractures, including as a result of CTIBL, as well as for the

- Zoledronic acid or denosumab should be started as soon as possible in all patients with bone metastases secondary to solid tumours, regardless of the presence or absence of symptoms
- Greater efficacy of denosumab over zoledronic acid has been demonstrated with respect to various classical pre-specified endpoints
- There is a lack of consensus regarding the optimal duration of zoledronic acid or denosumab treatment
- Continuous treatment is recommended for patients with progression of underlying bone metastases, a recent skeletal-related event, or elevated bone resorption markers*

Fig. 2. Key points from the 2014 European Society for Medical Oncology clinical practice guidelines [12]. * While the use of markers in decision making is controversial [133], there are biochemical studies supporting a therapy switch when bone markers remain elevated [134].

treatment of bone loss associated with hormone ablation in patients with breast or prostate cancer at increased risk of fractures [130]. It is important to note that discontinuation of denosumab in post-menopausal women with reduced BMD is associated with an increase in multiple vertebral fractures to the level observed in untreated participants [131]. Therefore, patients with osteoporosis who discontinue denosumab should transition to an alternative antiresorptive treatment. This transition should be not carried out until 7–8 months after the last denosumab injection, to ensure maintenance of BMD gains [132]. Furthermore, in women with breast cancer receiving aromatase inhibitors, the increase in fracture risk after discontinuing denosumab was negated in women who also discontinued their aromatase inhibitor therapy before, or within 6 months after, stopping denosumab [133]. These findings warrant further research to fully evaluate the risk of fracture in patients with cancer who discontinue denosumab.

Treatment guidelines and real-world treatment patterns

In 2014, the European Society for Medical Oncology (ESMO) published clinical practice guidelines on bone health in patients with cancer [12] (key points are summarised in Fig. 2 [134,135]). Treatment with ZA or denosumab was recommended in patients with bone metastases from either breast cancer or prostate cancer, irrespective of the presence or absence of symptoms. These agents were also recommended in patients with advanced lung cancer, renal cancer and other solid tumours with bone metastases, particularly those at high risk of SREs and a life expectancy of > 3 months [12]. The ESMO guidelines state that bisphosphonates or denosumab should be started as soon as metastatic bone disease is diagnosed and continued throughout the course of the disease [12], although this recommendation may not be followed in routine practice [136]. The ESMO guidelines are currently under revision and a new version is scheduled to be published in 2019.

In 2017, the American Society for Clinical Oncology (ASCO) and Cancer Care Ontario (CCO) published guidelines on bone modifying agents in metastatic breast cancer [137]. Like ESMO, they recommend treatment for all patients with evidence of metastases, although the ASCO-CCO guidelines include pamidronate as a recommended agent in addition to denosumab and ZA. They further note that patients with bone pain should receive analgesia in addition to denosumab or a bisphosphonate. Neither the ESMO nor ASCO-CCO guidelines address the

issue of whether bisphosphonate or denosumab treatment could be safely withdrawn in patients with a very small number of asymptomatic bone metastases, as life expectancy in these patients can be high [138] and treatment can place them at risk of ONJ and pathological femur fractures. Delaying treatment in these ‘low risk’ patients has not, however, been evaluated in controlled trials, and there are currently no predictive tools to assess the risk of such patients developing SREs.

In 2016, a consensus panel concluded that bisphosphonates for prevention of CTIBL should be part of routine clinical practice in all patients with either a bone density T-score of < -2.0 or two or more clinical fracture risk factors [139]. The authors noted, however, that bisphosphonates are not licensed for either indication.

The use of bisphosphonates and denosumab in clinical practice has been evaluated in several real-world data sets. Data from a German treatment registry showed that most patients (89%) with bone metastases from breast cancer receive treatment in line with guidelines, with bisphosphonates (primarily ZA) or denosumab started a median of 3 weeks after diagnosis of bone metastases [140]. Notably, data from the Adelphi Prostate Cancer and Breast Cancer Disease Specific Programmes showed that patients with breast cancer are more likely to receive bisphosphonate or denosumab treatment than those with prostate cancer [141]. (Body JJ et al. manuscript submitted). Overall, 11% of patients with breast cancer and 26% of those with prostate cancer did not receive any treatment with bisphosphonates or denosumab. Furthermore, in an analysis of 47,052 patients with solid tumours and bone metastases who had a minimum of 6 months of continuous enrolment in a health plan in the USA, 28,135 patients (60%) did not receive denosumab or an intravenous bisphosphonate within 6 months of their diagnosis of bone metastasis [142]. Thus it is clear that, while many patients in real-world clinical practice receive guideline-recommended treatment, there may be substantial differences between countries.

The future

Despite the advances made in the management of bone health in patients with cancer, there are still several off-label areas in which further research is needed (Fig. 3). As noted earlier, the optimal duration of therapy remains unclear [12,79,143]. Extended dosing intervals or intermittent therapy may be used in practice, and the published data comparing different ZA dosing schedules are described above [74–76]. Studies investigating 4-weekly vs 12-weekly administration of denosumab are also underway (ClinicalTrials.gov: NCT02721433; NCT02051218 [103]). Additional areas in which research is needed include strategies to optimise the risk–benefit ratio of treatment with bisphosphonates and denosumab, and their use in patients with very severe disease.

In recent years, developments in imaging and molecular analysis have allowed greater characterisation of the microenvironment within bone that allows metastases to develop (the ‘metastatic niche’) [144]. This microenvironment is actively modified by the primary tumour before metastasis occurs [145]. When tumour cells first colonise bone, they enter a dormant state before subsequently being reactivated by mechanisms including osteoclast-mediated modelling of the endosteal bone surface. This process represents a potential target for future therapeutic intervention, as well as a means of improving risk stratification [144,146]. The precise mechanisms that underly dormancy and reactivation, however, remain to be discovered, and may vary between cancer types [147].

There are limited data on efficacy and safety of bisphosphonates and denosumab in patients with bone metastases arising from other solid tumours such as melanoma, renal cell carcinoma and colon cancer. In these patients, and in those with lung cancer, use of targeted therapy and immunotherapy has led to an increase in life expectancy [148–151]. Data so far suggest that denosumab may have the potential to enhance the effects of immunotherapy without increasing adverse

- Optimal time to start bisphosphonate or denosumab therapy in patients with bone metastases, based on risk of skeletal related events
- Optimal duration of bisphosphonate and denosumab therapy based on risk/benefit ratio
- Optimal dose frequency
- Use of bisphosphonates and denosumab in patients with other solid tumours except breast and prostate (e.g. lung, colon or melanoma)
- Potential synergistic action of denosumab with other agents
- The potential role of bisphosphonates in the prevention of cancer therapy-induced bone loss
- Exploration of novel therapy approaches (e.g. use of bone-forming agents)
- Data on economic and patient-oriented outcomes in patients receiving bisphosphonates and denosumab

Fig. 3. Areas where further research is needed with regard to management of bone health in patients with solid tumours.

event burden, including in non-small-lung cancer [152–155]. Moreover, the combination of denosumab with immunotherapy is in clinical use in patients with non-small-lung cancer and bone metastases (RvM, personal communication), and is also being evaluated in ongoing trials such as DENIVOS (ClinicalTrials.gov: NCT03669523). Denosumab may also have additive actions with novel biologic agents such as: crizotinib or other ALK inhibitors; erlotinib; gefitinib; afatinib; CTLA4, PD-1 and PD-L1 inhibitors; and c-Met inhibitors [81,156,157]. Trials involving PD-1 and PD-L1 inhibitors in combination with denosumab in patients with solid tumours are underway, such as the DENIVOS study mentioned above, as well as the KEYPAD study in clear cell renal carcinoma (ClinicalTrials.gov: NCT03280667) and the CHARLI study in melanoma (ClinicalTrials.gov: NCT03161756).

Radium-223 is used for the management of bone metastases in men with CRPC and no known visceral metastases (Supplementary Table 1), and data show that it can delay SREs and improve overall survival [158]. Notably, sub-analysis of the pivotal ALSYMPCA trial showed that concomitant bisphosphonate use was a significant predictor for reduced risk of SRE in men with CRPC receiving radium-223 [48]. Data from an open-label, uncontrolled, early access programme suggested that survival benefits were significantly greater when radium-223 was combined with enzalutamide and/or abiraterone, or with denosumab, compared with radium-223 alone [159]. Recently presented data from the ERA-223 study, however, suggest that combination of radium-223 with abiraterone plus prednisone/prednisolone did not improve either symptomatic SRE-free survival or overall survival, and was associated with an increased risk of fractures [160]. The fracture rate was, however, lower in men who were also receiving denosumab or a bisphosphonate. As a result, only those participants who were receiving denosumab or a bisphosphonate, regardless of allocated treatment arm, were allowed to continue the study (patients who started the study without receiving denosumab or a bisphosphonate were not allowed to start one after randomization). Although this bone-protective effect was not prospectively evaluated, these data suggest that bisphosphonates and denosumab are important therapeutic tools irrespective of the specific anti-cancer treatment used.

Although there are many novel agents under development for

advanced cancer that may also have wider effects on bone, there are few trials in progress evaluating new therapies that specifically target the bone microenvironment. More research is also needed into the use of bone-forming (anabolic) agents in patients with bone metastases, as there are currently no drugs licensed for use in solid tumours that increase bone formation. In most cancers, including breast cancer and multiple myeloma, though not prostate cancer, bone formation is reduced and lytic bone metastases often predominate [161,162]. Given that denosumab is a highly potent anti-resorptive agent, the need for new anabolic agents is greater than that for novel anti-resorptives. Bone anabolic agents with potential for treatment of patients with bone metastases include everolimus, proteasome inhibitors, sotatercept, and anti-WNT, DKK1, and sclerostin antibodies such as romosozumab [163], although data on these new agents are currently lacking.

Summary and conclusions

Patients with solid tumours are at risk of bone metastases, which have a severe impact on morbidity and mortality, and also lead to substantial increases in healthcare resource utilisation and costs. Nonetheless, many patients with solid tumours and bone metastases are not currently protected from bone complications. Bisphosphonates and denosumab have an important role in the management of bone health in patients with solid tumours, in terms of reducing the frequency of complications associated with existing bone metastases and, in the case of denosumab, in the management of CTIBL. In patients with bone metastases, ZA and denosumab have been shown to reduce the incidence of SREs. Treatment also delays the onset of bone pain in patients for whom bone metastasis is the most common cause of pain, and early initiation of treatment is important to maximise both efficacy and pain control. Superiority of denosumab over ZA has been demonstrated in an integrated analysis of solid tumour trials for prevention of SREs, reduction in bone pain and improvement of quality of life, with associated benefits for patients, healthcare systems and society. In patients with breast cancer receiving hormonal therapy, ZA and denosumab can prevent bone loss and maintain BMD, and denosumab can also prevent CTIBL in breast and prostate cancer. Denosumab, but not ZA, is licensed for these indications. Areas in which further research is necessary include length of therapy, management of side effects, particularly in the long term, and the potential differences in risk of SREs over time in different tumour types.

Acknowledgements

Role of funding source

Medical writing assistance was provided by Dan Booth PhD (Bioscript Medical Ltd, Macclesfield, UK) and funded by Amgen (Europe) GmbH (Rotkreuz, Switzerland).

Conflict of interest

Roger von Moos has received research grants from Amgen and Bayer, has consulted for Amgen, Bayer, GlaxoSmithKline, Roche, BMS, MSD and Novartis and has received honoraria from Amgen, Bayer and GlaxoSmithKline.

Luis Costa has received research grants from Amgen, Bayer, Novartis and Roche, and speaker honoraria from Amgen, Bayer, Janssen, Lilly and Roche, and is a consultant for Amgen, Novartis and Servier.

Eva Gonzalez-Suarez has received speaker and consulting fees from Amgen. Her laboratory is funded by the Spanish Ministry of Economy and Competitiveness MINECO SAF2017-86117-R, co-funded by FEDER funds/European Regional Development Fund (ERDF) – a way to build Europe – and European Union ERC-2015 – Consolidator Grant LS4-682935.

Evangelos Terpos has received honoraria from Amgen, BMS,

Celgene, Genesis, Janssen and Takeda, is a member of steering committees for Amgen, Janssen and Takeda; and is a member of a data-monitoring committee for Celgene.

Daniela Niepel is an employee of Amgen (Europe) GmbH.

Jean-Jacques Body has received speaker and consulting fees from Amgen and Sandoz, and consulting fees from Bayer.

Author contributions

All authors were involved in the drafting and review of the manuscript and approved the final version for submission.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ctrv.2019.05.003>.

References

- [1] Gdowski AS, Ranjan A, Vishwanatha JK. Current concepts in bone metastasis, contemporary therapeutic strategies and ongoing clinical trials. *J Exp Clin Cancer Res* 2017;36:108.
- [2] Macedo F, Ladeira K, Pinho F, Saraiva N, Bonito N, Pinto L, et al. Bone metastases: an overview. *Oncol Rev* 2017;11:321.
- [3] Svensson E, Christiansen CF, Ulrichsen SP, Rorth MR, Sorensen HT. Survival after bone metastasis by primary cancer type: a Danish population-based cohort study. *BMJ Open* 2017;7:e016022.
- [4] Hernandez RK, Wade SW, Reich A, Piroli M, Liede A, Lyman GH. Incidence of bone metastases in patients with solid tumors: analysis of oncology electronic medical records in the United States. *BMC Cancer* 2018;18:44.
- [5] Body JJ, Quinn G, Talbot S, Booth E, Demonty G, Taylor A, et al. Systematic review and meta-analysis on the proportion of patients with breast cancer who develop bone metastases. *Crit Rev Oncol Hematol* 2017;115:67–80.
- [6] Casimiro S, Ferreira AR, Mansinho A, Alho I, Costa L. Molecular mechanisms of bone metastasis: which targets came from the bench to the bedside? *Int J Mol Sci* 2016;17.
- [7] Costa L, Badia X, Chow E, Lipton A, Wardley A. Impact of skeletal complications on patients' quality of life, mobility, and functional independence. *Support Care Cancer* 2008;16:879–89.
- [8] Delea T, McKiernan J, Brandman J, Edelsberg J, Sung J, Raut M, et al. Retrospective study of the effect of skeletal complications on total medical care costs in patients with bone metastases of breast cancer seen in typical clinical practice. *J Support Oncol* 2006;4:341–7.
- [9] Hagiwara M, Delea TE, Chung K. Healthcare costs associated with skeletal-related events in breast cancer patients with bone metastases. *J Med Econ* 2014;17:223–30.
- [10] Hagiwara M, Delea TE, Saville MW, Chung K. Healthcare utilization and costs associated with skeletal-related events in prostate cancer patients with bone metastases. *Prostate Cancer Prostatic Dis* 2013;16:23–7.
- [11] Body JJ, Chevalier P, Gunther O, Hechmati G, Lamotte M. The economic burden associated with skeletal-related events in patients with bone metastases secondary to solid tumors in Belgium. *J Med Econ* 2013;16:539–46.
- [12] Coleman R, Body JJ, Aapro M, Hadji P, Herrstedt J. Esmo guidelines working group. Bone health in cancer patients: Esmo clinical practice guidelines. *Ann Oncol* 2014;25(Suppl 3). iii124–37.
- [13] Bayer plc. Bonfos. Summary of Product Characteristics. Reading: Bayer plc; 2017.
- [14] Bedford Laboratories. Pamidronate disodium. Prescribing Information. Bedford, OH: Bedford Laboratories™; 2014.
- [15] medac GmbH. Disodium pamidronate. Summary of Product Characteristics. Wedel: medac; 2017.
- [16] Roche Products Limited. Bondronat film-coated tablets. Summary of Product Characteristics. Welwyn Garden City: Roche Registration Limited; 2016.
- [17] Roche Products Limited. Bondronat concentrate for solution for infusion. Summary of Product Characteristics. Welwyn Garden City: Roche Registration Limited; 2016.
- [18] Novartis Pharmaceuticals. Zometa. Summary of Product Characteristics. Cambridge: Novartis Europharm Limited; 2006.
- [19] Novartis Pharmaceuticals. Zometa. Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2016.
- [20] Amgen. Xgeva. Summary of Product Characteristics. Breda: Amgen Europe B.V.; 2016.
- [21] Amgen. Xgeva. Prescribing Information. Thousand Oaks, CA: Amgen Inc; 2013.
- [22] Bayer. Xofigo. Summary of Product Characteristics. Reading: Bayer plc; 2017.
- [23] Bayer. Xofigo. Prescribing Information. Wayne, NJ: Bayer Healthcare Pharmaceuticals Inc; 2013.
- [24] Paterson AH, Powles TJ, Kanis JA, McCloskey E, Hanson J, Ashley S. Double-blind controlled trial of oral clodronate in patients with bone metastases from breast cancer. *J Clin Oncol* 1993;11:59–65.
- [25] Elomaa I, Kymala T, Tammela T, Viitanen J, Ottelin J, Ruutu M, et al. Effect of oral clodronate on bone pain. A controlled study in patients with metastatic prostate cancer. *Int Urol Nephrol* 1992;24:159–66.
- [26] Kymala T, Taube T, Tammela TL, Risteli L, Risteli J, Elomaa I. Concomitant i.v. and oral clodronate in the relief of bone pain – a double-blind placebo-controlled study in patients with prostate cancer. *Br J Cancer* 1997;76:939–42.
- [27] Dearnaley DP, Mason MD, Parmar MK, Sanders K, Sydes MR. Adjuvant therapy with oral sodium clodronate in locally advanced and metastatic prostate cancer: long-term overall survival results from the MRC PR04 and PR05 randomised controlled trials. *Lancet Oncol* 2009;10:872–6.
- [28] Hortobagyi GN, Theriault RL, Porter L, Blayney D, Lipton A, Sinoff C, et al. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer Study Group. *N Engl J Med* 1996;335:1785–91.
- [29] Theriault RL, Lipton A, Hortobagyi GN, Leff R, Gluck S, Stewart JF, et al. Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: a randomized, placebo-controlled trial. Protocol 18 Aredia Breast Cancer Study Group. *J Clin Oncol* 1999;17:846–54.
- [30] Rosen LS, Gordon D, Kaminski M, Howell A, Belch A, Mackey J, et al. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial. *Cancer J* 2001;7:377–87.
- [31] Rosen LS, Gordon D, Kaminski M, Howell A, Belch A, Mackey J, et al. Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. *Cancer* 2003;98:1735–44.
- [32] Berenson JR, Rosen LS, Howell A, Porter L, Coleman RE, Morley W, et al. Zoledronic acid reduces skeletal-related events in patients with osteolytic metastases. *Cancer* 2001;91:1191–200.
- [33] Rosen LS, Gordon DH, Dugan Jr. W, Major P, Eisenberg PD, Provencher L, et al. Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. *Cancer* 2004;100:36–43.
- [34] Barrett-Lee P, Casbard A, Abraham J, Hood K, Coleman R, Simmonds P, et al. Oral ibandronic acid versus intravenous zoledronic acid in treatment of bone metastases from breast cancer: a randomised, open label, non-inferiority phase 3 trial. *Lancet Oncol* 2014;15:114–22.
- [35] 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. *J Natl Cancer Inst* 2002;94:1458–68.
- [36] 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. *J Natl Cancer Inst* 2004;96:879–82.
- [37] Rosen LS, Gordon D, Tchekmedyian S, Yanagihara R, Hirsh V, Krzakowski M, et al. Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: a phase III, double-blind, randomized trial—the Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. *J Clin Oncol* 2003;21:3150–7.
- [38] Rosen LS, Gordon D, Tchekmedyian NS, Yanagihara R, Hirsh V, Krzakowski M, et al. Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors: a randomized, phase III, double-blind, placebo-controlled trial. *Cancer* 2004;100:2613–21.
- [39] Body JJ, Diel IJ, Lichinitser MR, Kreuser ED, Dornoff W, Gorbunova VA, et al. Intravenous ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases. *Ann Oncol* 2003;14:1399–405.
- [40] Body JJ, Diel IJ, Lichinitser M, Lazarev A, Pecherstorfer M, Bell R, et al. Oral ibandronate reduces the risk of skeletal complications in breast cancer patients with metastatic bone disease: results from two randomised, placebo-controlled phase III studies. *Br J Cancer* 2004;90:1133–7.
- [41] Stopeck AT, Lipton A, Body JJ, Steger GG, Tonkin K, de Boer RH, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. *J Clin Oncol* 2010;28:5132–9.
- [42] Fizazi K, Carducci M, Smith M, Damiao R, Brown J, Karsh L, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet* 2011;377:813–22.
- [43] Henry DH, Costa L, Goldwasser F, Hirsh V, Hungria V, Prausova J, et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *J Clin Oncol* 2011;29:1125–32.
- [44] Henry D, Vadhan-Raj S, Hirsh V, von Moos R, Hungria V, Costa L, et al. Delaying skeletal-related events in a randomized phase 3 study of denosumab versus zoledronic acid in patients with advanced cancer: an analysis of data from patients with solid tumors. *Support Care Cancer* 2014;22:679–87.
- [45] Scagliotti GV, Hirsh V, Siena S, Henry DH, Woll PJ, Manegold C, et al. Overall survival improvement in patients with lung cancer and bone metastases treated with denosumab versus zoledronic acid: subgroup analysis from a randomized phase 3 study. *J Thorac Oncol* 2012;7:1823–9.
- [46] Nilsson S, Franzen L, Parker C, Tyrrell C, Blom R, Tennvall J, et al. Bone-targeted radium-223 in symptomatic, hormone-refractory prostate cancer: a randomised, multicentre, placebo-controlled phase II study. *Lancet Oncol* 2007;8:587–94.
- [47] Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fosså SD, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med* 2013;369:213–23.

- [48] 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. *Lancet Oncol* 2014;15:738–46.
- [49] Todenhofer T, Stenzl A, Hofbauer LC, Rachner TD. Targeting bone metabolism in patients with advanced prostate cancer: current options and controversies. *Int J Endocrinol* 2015;2015:838202.
- [50] Rizzoli R, Body JJ, DeCensi A, Reginster JY, Piscitelli P, Brandi ML, et al. Guidance for the prevention of bone loss and fractures in postmenopausal women treated with aromatase inhibitors for breast cancer: an ESO position paper. *Osteoporos Int* 2012;23:2567–76.
- [51] Russell RG. Bisphosphonates: the first 40 years. *Bone* 2011;49:2–19.
- [52] Bock O, Felsenberg D. Bisphosphonates in the management of postmenopausal osteoporosis—optimizing efficacy in clinical practice. *Clin Interv Aging* 2008;3:279–97.
- [53] Gravalos C, Rodriguez C, Sabino A, Segui MA, Virizuela JA, Carmona A, et al. SEOM Clinical Guideline for bone metastases from solid tumours (2016). *Clin Transl Oncol* 2016;18:1243–53.
- [54] Elomaa I, Blomqvist C, Porkka L, Lamberg-Allardt C, Borgstrom GH. Treatment of skeletal disease in breast cancer: a controlled clodronate trial. *Bone* 1987;8(Suppl 1):S53–6.
- [55] van Holten-Verzantvoort AT, Kroon HM, Bijvoet OL, Cleton FJ, Beex LV, Blijham G, et al. Palliative pamidronate treatment in patients with bone metastases from breast cancer. *J Clin Oncol* 1993;11:491–8.
- [56] Costa L, Moreira C, da Costa EB. [Disodium pamidronate (APD) in the treatment of bone metastases]. *Acta Med Port* 1993;6:71–3.
- [57] Conte PF, Giannesi PG, Latreille J, Mauriac L, Koliren L, Calabresi F, et al. Delayed progression of bone metastases with pamidronate therapy in breast cancer patients: a randomized, multicenter phase III trial. *Ann Oncol* 1994;5(Suppl 7):S41–4.
- [58] Paterson AH. Should bisphosphonates be standard therapy for bone pain? *Support Care Cancer* 1997;5:200–4.
- [59] Russell RG, Rogers MJ. Bisphosphonates: from the laboratory to the clinic and back again. *Bone* 1999;25:97–106.
- [60] Body JJ, Coleman RE, Piccart M. Use of bisphosphonates in cancer patients. *Cancer Treat Rev* 1996;22:265–87.
- [61] Lipton A, Theriault RL, Hortobagyi GN, Simeone J, Knight RD, Mellars K, et al. Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. *Cancer* 2000;88:1082–90.
- [62] Conte P, Guarneri V. Safety of intravenous and oral bisphosphonates and compliance with dosing regimens. *Oncologist* 2004;9(Suppl 4):28–37.
- [63] Rosini S, Rosini S, Bertoldi I, Frediani B. Understanding bisphosphonates and osteonecrosis of the jaw: uses and risks. *Eur Rev Med Pharmacol Sci* 2015;19:3309–17.
- [64] Green JR, Muller K, Jaeggi KA. Preclinical pharmacology of CGP 42446, a new, potent, heterocyclic bisphosphonate compound. *J Bone Miner Res* 1994;9:745–51.
- [65] Aft R, Naughton M, Trinkaus K, Watson M, Ylagan L, Chavez-MacGregor M, et al. Effect of zoledronic acid on disseminated tumour cells in women with locally advanced breast cancer: an open label, randomised, phase 2 trial. *Lancet Oncol* 2010;11:421–8.
- [66] Green JR. Bisphosphonates: preclinical review. *Oncologist* 2004;9(Suppl 4):3–13.
- [67] Denoyelle C, Hong L, Vannier JP, Soria J, Soria C. New insights into the actions of bisphosphonate zoledronic acid in breast cancer cells by dual RhoA-dependent and -independent effects. *Br J Cancer* 2003;88:1631–40.
- [68] Gnant M. The evolving role of zoledronic acid in early breast cancer. *Onco Targets Ther* 2009;2:95–104.
- [69] Body JJ, Lortholary A, Romieu G, Vigneron AM, Ford J. A dose-finding study of zoledronate in hypercalcemic cancer patients. *J Bone Miner Res* 1999;14:1557–61.
- [70] Smith MR, Halabi S, Ryan CJ, Hussain A, Vogelzang N, Stadler 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). *J Clin Oncol* 2014;32:1143–50.
- [71] Hirsh V, Major PP, Lipton A, Cook RJ, Langer CJ, Smith MR, et al. Zoledronic acid and survival in patients with metastatic bone disease from lung cancer and elevated markers of osteoclast activity. *J Thorac Oncol* 2008;3:228–36.
- [72] Coleman RE, Lipton A, Costa L, Cook RJ, Lee KA, Saad F, et al. Possible survival benefits from zoledronic acid treatment in patients with bone metastases from solid tumours and poor prognostic features – an exploratory analysis of placebo-controlled trials. *J Bone Oncol* 2013;2:70–6.
- [73] Terpos E, Kleber M, Engelhardt M, Zweegman S, Gay F, Kastiris E, et al. European Myeloma Network guidelines for the management of multiple myeloma-related complications. *Haematologica* 2015;100:1254–66.
- [74] Amadori D, Aglietta M, Alessi B, Gianni L, Ibrahim T, Farina G, et al. Efficacy and safety of 12-weekly versus 4-weekly zoledronic acid for prolonged treatment of patients with bone metastases from breast cancer (ZOOM): a phase 3, open-label, randomised, non-inferiority trial. *Lancet Oncol* 2013;14:663–70.
- [75] Hortobagyi GN, Van Poznak C, Harker WG, Gradishar WJ, Chew H, Dakhil SR, et al. Continued treatment effect of zoledronic acid dosing every 12 vs 4 weeks in women with breast cancer metastatic to bone: the OPTIMIZE-2 randomized clinical trial. *JAMA Oncol* 2017;3:906–12.
- [76] Himelstein AL, Foster JC, Khatcheressian JL, Roberts JD, Seisler DK, Novotny PJ, et al. Effect of longer-interval vs standard dosing of zoledronic acid on skeletal events in patients with bone metastases: a randomized clinical trial. *JAMA* 2017;317:48–58.
- [77] Body JJ, Lichinitser M, Tjulandin S, Garnero P, Bergstrom B. Oral ibandronate is as active as intravenous zoledronic acid for reducing bone turnover markers in women with breast cancer and bone metastases. *Ann Oncol* 2007;18:1165–71.
- [78] Costa L. Which bisphosphonate to treat bone metastases? *Lancet Oncol* 2014;15:15–6.
- [79] Biskup E, Cai F, Vetter M. Bone targeted therapies in advanced breast cancer. *Swiss Med Wkly* 2017;147:w14440.
- [80] Body JJ. Zoledronic acid: an advance in tumour bone disease therapy and a new hope for osteoporosis. *Expert Opin Pharmacother* 2003;4:567–80.
- [81] De Castro J, Garcia R, Garrido P, Isla D, Massuti B, Blanca B, et al. Therapeutic potential of denosumab in patients with lung cancer: beyond prevention of skeletal complications. *Clin Lung Cancer* 2015;16:431–46.
- [82] Lipton A. Future treatment of bone metastases. *Clin Cancer Res* 2006;12:6305s–8s.
- [83] Body JJ. Denosumab for the management of bone disease in patients with solid tumors. *Expert Rev Anticancer Ther* 2012;12:307–22.
- [84] Brown JE, Coleman RE. Denosumab in patients with cancer—a surgical strike against the osteoclast. *Nat Rev Clin Oncol* 2012;9:110–8.
- [85] Faget J, Contat C, Zangger N, Peters S, Meylan E. RANKL signaling sustains primary tumor growth in genetically engineered mouse models of lung adenocarcinoma. *J Thorac Oncol* 2018;13:387–98.
- [86] Rao S, Sigl V, Wimmer RA, Novatchkova M, Jais A, Wagner G, et al. RANK rewires energy homeostasis in lung cancer cells and drives primary lung cancer. *Genes Dev* 2017;31:2099–112.
- [87] Gonzalez-Suarez E, Jacob AP, Jones J, Miller R, Roudier-Meyer MP, Erwert R, et al. RANK ligand mediates progesterin-induced mammary epithelial proliferation and carcinogenesis. *Nature* 2010;468:103–7.
- [88] Palafox M, Ferrer I, Pellegrini P, Vila S, Hernandez-Ortega S, Urruticoechea A, et al. RANK induces epithelial-mesenchymal transition and stemness in human mammary epithelial cells and promotes tumorigenesis and metastasis. *Cancer Res* 2012;72:2879–88.
- [89] Lacey DL, Boyle WJ, Simonet WS, Kostenuik PJ, Dougall WC, Sullivan JK, et al. Bench to bedside: elucidation of the OPG-RANK-RANKL pathway and the development of denosumab. *Nat Rev Drug Discov* 2012;11:401–19.
- [90] Schramek D, Leibbrandt A, Sigl V, Kenner L, Pospisilik JA, Lee HJ, et al. Osteoclast differentiation factor RANKL controls development of progesterin-driven mammary cancer. *Nature* 2010;468:98–102.
- [91] Nolan E, Vaillant F, Branstetter D, Pal B, Giner G, Whitehead L, et al. RANK ligand as a potential target for breast cancer prevention in BRCA1-mutation carriers. *Nat Med* 2016;22:933–9.
- [92] Sigl V, Owusu-Boaitey K, Joshi PA, Kavirayani A, Wirsberger G, Novatchkova M, et al. RANKL/RANK control Brca1 mutation. *Cell Res* 2016;26:761–74.
- [93] Yoldi G, Pellegrini P, Trinidad EM, Cordero A, Gomez-Miragaya J, Serra-Musach J, et al. RANK signaling blockade reduces breast cancer recurrence by inducing tumor cell differentiation. *Cancer Res* 2016;76:5857–69.
- [94] Pellegrini P, Cordero A, Gallego MI, Dougall WC, Munoz P, Pujana MA, et al. Constitutive activation of RANK disrupts mammary cell fate leading to tumorigenesis. *Stem Cells* 2013;31:1954–65.
- [95] Tanos T, Sfomios G, Echeverria PC, Ayyanan A, Gutierrez M, Delaloye JF, et al. Progesterone/RANKL is a major regulatory axis in the human breast. *Sci Transl Med* 2013;5:182ra55.
- [96] Body JJ, Facon T, Coleman RE, Lipton A, Geurs F, Fan M, et al. A study of the biological receptor activator of nuclear factor-kappaB ligand inhibitor, denosumab, in patients with multiple myeloma or bone metastases from breast cancer. *Clin Cancer Res* 2006;12:1221–8.
- [97] 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. *Eur J Cancer* 2012;48:3082–92.
- [98] von Moos R, Body JJ, Egerdie B, Stopeck A, Brown JE, Dmyanov D, et al. Pain and health-related quality of life in patients with advanced solid tumours and bone metastases: integrated results from three randomized, double-blind studies of denosumab and zoledronic acid. *Support Care Cancer* 2013;21:3497–507.
- [99] Sun L, Yu S. Efficacy and safety of denosumab versus zoledronic acid in patients with bone metastases: a systematic review and meta-analysis. *Am J Clin Oncol* 2013;36:399–403.
- [100] Hechmati G, Hauber AB, Arellano J, Mohamed AF, Qian Y, Gatta F, et al. Patients' preferences for bone metastases treatments in France, Germany and the United Kingdom. *Support Care Cancer* 2015;23:21–8.
- [101] Body JJ, Gatta F, De Cock E, Tao S, Kritikou P, Wimberger P, et al. An observational time and motion study of denosumab subcutaneous injection and zoledronic acid intravenous infusion in patients with metastatic bone disease: results from three European countries. *Support Care Cancer* 2017;25:2823–32.
- [102] Chen F, Pu F. Safety of denosumab versus zoledronic acid in patients with bone metastases: a meta-analysis of randomized controlled trials. *Oncol Res Treat* 2016;39:453–9.
- [103] von Moos R, Hawle H, Hayoz S, Cathomas R, Müller A, Schmid S, et al. Incidence of hypocalcaemia in a non-inferiority phase III trial assessing prevention of symptomatic skeletal events (SSE) with denosumab (DN) administered every 4 weeks (q4w) versus every 12 weeks (q12w): SAKK 96/12 (REDUSE). *Ann Oncol* 2018;29(Suppl 8). (Abstract 1703P).
- [104] Brown-Glaberman U, Stopeck AT. Role of denosumab in the management of skeletal complications in patients with bone metastases from solid tumors. *Biologics* 2012;6:89–99.
- [105] Body JJ, Bone HG, de Boer RH, Stopeck A, Van Poznak C, Damiao R, et al. Hypocalcaemia in patients with metastatic bone disease treated with denosumab. *Eur J Cancer* 2015;51:1812–21.
- [106] Schiodt M, Vadhan-Raj S, Chambers MS, Nicolatou-Galitis O, Politis C, Coropciuc

- R, et al. A multicenter case registry study on medication-related osteonecrosis of the jaw in patients with advanced cancer. *Support Care Cancer* 2018;26:1905–15.
- [107] Otto S, Pautke C, Van den Wyngaert T, Niepel D, Schioldt M. Medication-related osteonecrosis of the jaw: prevention, diagnosis and management in patients with cancer and bone metastases. *Cancer Treat Rev* 2018;69:177–87.
- [108] Nicolatou-Galitis O, Schioldt M, Mendes RA, Ripamonti C, Hope S, Drudge-Coates L, et al. Medication-related osteonecrosis of the jaw: definition and best practice for prevention, diagnosis, and treatment. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2018. Epub ahead of print.
- [109] Hechmati G, Cure S, Gouepo A, Hoefeler H, Lorusso V, Luftner D, et al. Cost of skeletal-related events in European patients with solid tumours and bone metastases: data from a prospective multinational observational study. *J Med Econ* 2013;16:691–700.
- [110] McDougall JA, Bansal A, Goulart BH, McCune JS, Karnopp A, Fedorenko C, et al. The clinical and economic impacts of skeletal-related events among Medicare enrollees with prostate cancer metastatic to bone. *Oncologist* 2016;21:320–6.
- [111] Cristino J, Finek J, Jandova P, Kolek M, Pásztor B, Giannopoulou C, et al. Cost-effectiveness of denosumab versus zoledronic acid for preventing skeletal-related events in the Czech Republic. *J Med Econ* 2017;20:799–812.
- [112] Terpos E, Jamotte A, Christodouloupolou A, Campioni M, Bhowmik D, Kennedy L, et al. A cost-effectiveness analysis of denosumab for the prevention of skeletal-related events in patients with multiple myeloma in four European countries: Austria, Belgium, Greece, and Italy. *J Med Econ* 2019. Epub ahead of print.
- [113] Shapiro CL, Moriarty JP, Dusetzina S, Himmelstein AL, Foster JC, Grubbs SS, et al. Cost-effectiveness analysis of monthly zoledronic acid, zoledronic acid every 3 months, and monthly denosumab in women with breast cancer and skeletal metastases: CALGB 70604 (alliance). *J Clin Oncol* 2017;35:3949–55.
- [114] Kennedy L, Bhatta S, Hechmati G, Buchanan J. Response to cost-effectiveness analysis of zoledronic acid once per month, zoledronic acid once every 3 months, and denosumab once per month in women with breast cancer and skeletal metastases. *J Clin Oncol* 2018;36:1051.
- [115] Van Poznak C, Hannon RA, Mackey JR, Campone M, Appfelstaedt JP, Clack G, et al. Prevention of aromatase inhibitor-induced bone loss using risedronate: the SABRE trial. *J Clin Oncol* 2010;28:967–75.
- [116] Lester JE, Dodwell D, Purohit OP, Gutcher SA, Ellis SP, Thorpe R, et al. Prevention of anastrozole-induced bone loss with monthly oral ibandronate during adjuvant aromatase inhibitor therapy for breast cancer. *Clin Cancer Res* 2008;14:6336–42.
- [117] Serpa Neto A, Tobias-Machado M, Esteves MA, Senra MD, Wroclawski ML, Fonseca FL, et al. Bisphosphonate therapy in patients under androgen deprivation therapy for prostate cancer: a systematic review and meta-analysis. *Prostate Cancer Prostatic Dis* 2012;15:36–44.
- [118] Llombart A, Frassoldati A, Paija O, Sleeboom HP, Jerusalem G, Mebis J, et al. Immediate administration of zoledronic acid reduces aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer: 12-month analysis of the E-ZO-FAST trial. *Clin Breast Cancer* 2012;12:40–8.
- [119] Brufsky AM, Harker WG, Beck JT, Bosserman L, Vogel C, Seidler C, et al. Final 5-year results of Z-FAST trial: adjuvant zoledronic acid maintains bone mass in postmenopausal breast cancer patients receiving letrozole. *Cancer* 2012;118:1192–201.
- [120] Brufsky A, Bundred N, Coleman R, Lambert-Falls R, Mena R, Hadji P, et al. Integrated analysis of zoledronic acid for prevention of aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole. *Oncologist* 2008;13:503–14.
- [121] Coleman R, de Boer R, Eidtmann H, Llombart A, Davidson N, Neven P, et al. Zoledronic acid (zoledronate) for postmenopausal women with early breast cancer receiving adjuvant letrozole (ZO-FAST study): final 60-month results. *Ann Oncol* 2013;24:398–405.
- [122] Bundred NJ, Campbell ID, Davidson N, DeBoer RH, Eidtmann H, Monnier A, et al. Effective inhibition of aromatase inhibitor-associated bone loss by zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: ZO-FAST Study results. *Cancer* 2008;112:1001–10.
- [123] James ND, Sydes MR, Clarke NW, Mason MD, Deaneley DP, Spears MR, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multi-arm, multistage, platform randomised controlled trial. *Lancet* 2016;387:1163–77.
- [124] 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. *J Urol* 2003;169:2008–12.
- [125] Ellis GK, Bone HG, Chlebowski R, Paul D, Spadafora S, Smith J, et al. Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for non-metastatic breast cancer. *J Clin Oncol* 2008;26:4875–82.
- [126] Gnani M, Pfeiler G, Dubsky PC, Hubalek M, Greil R, Jakesz R, et al. Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet* 2015;386:433–43.
- [127] Smith MR, Egerdie B, Hernandez Toriz N, Feldman R, Tammela TL, Saad F, et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *N Engl J Med* 2009;361:745–55.
- [128] Denham JW, Joseph D, Lamb DS, Spry NA, Duchesne G, Matthews J, et al. Short-term androgen suppression and radiotherapy versus intermediate-term androgen suppression and radiotherapy, with or without zoledronic acid, in men with locally advanced prostate cancer (TROG 03.04 RADAR): an open-label, randomised, phase 3 factorial trial. *Lancet Oncol* 2014;15:1076–89.
- [129] Denham JW, Nowitz M, Joseph D, Duchesne G, Spry NA, Lamb DS, et al. Impact of androgen suppression and zoledronic acid on bone mineral density and fractures in the Trans-Tasman Radiation Oncology Group (TROG) 03.04 Randomised Androgen Deprivation and Radiotherapy (RADAR) randomised controlled trial for locally advanced prostate cancer. *BJU Int* 2014;114:344–53.
- [130] Amgen. Prolia. Summary of Product Characteristics. Breda: Amgen Europe B.V.; 2017.
- [131] Cummings SR, Ferrari S, Eastell R, Gilchrist N, Jensen JB, McClung M, et al. Vertebral fractures after discontinuation of denosumab: a post hoc analysis of the randomized placebo-controlled FREEDOM trial and its extension. *J Bone Miner Res* 2018;33:190–8.
- [132] Horne AM, Mihov B, Reid IR. Bone loss after romosozumab/denosumab: effects of bisphosphonates. *Calcif Tissue Int* 2018;103:55–61.
- [133] Pfeiler G, Steger GG, Egle D, Greil R, Fitzal F, Wette V, et al. Fracture risk after stopping adjuvant denosumab in hormone receptor positive breast cancer patients on aromatase inhibitor therapy – an analysis of 3,425 postmenopausal patients in the Phase III ABCSG-18 trial. *J Bone Miner Res* 2018;33(suppl 1):55. (Abstract #LB-1167).
- [134] Coleman R, Costa L, Saad F, Cook R, Hadji P, Terpos E, et al. Consensus on the utility of bone markers in the malignant bone disease setting. *Crit Rev Oncol Hematol* 2011;80:411–32.
- [135] Body JJ, Lipton A, Gralow J, Steger GG, Gao G, Yeh H, et al. Effects of denosumab in patients with bone metastases with and without previous bisphosphonate exposure. *J Bone Miner Res* 2010;25:440–6.
- [136] Lebrecht T, Casas A, Cavo M, Woll PJ, Deleplace C, Kennedy C, et al. The use of bisphosphonates in the management of bone involvement from solid tumours and haematological malignancies – a European survey. *Eur J Cancer Care (Engl)* 2017;26.
- [137] Van Poznak C, Somerfield MR, Barlow WE, Biermann JS, Bosserman LD, Clemons MJ, et al. Role of bone-modifying agents in metastatic breast cancer: an American Society of Clinical Oncology-Cancer Care Ontario Focused Guideline Update. *J Clin Oncol* 2017;35:3978–86.
- [138] Niikura N, Liu J, Hayashi N, Palla SL, Tokuda Y, Hortobagyi GN, et al. Treatment outcome and prognostic factors for patients with bone-only metastases of breast cancer: a single-institution retrospective analysis. *Oncologist* 2011;16:155–64.
- [139] Hadji P, Coleman RE, Wilson C, Powles TJ, Clezardin P, Aapro M, et al. Adjuvant bisphosphonates in early breast cancer: consensus guidance for clinical practice from a European Panel. *Ann Oncol* 2016;27:379–90.
- [140] Schroder J, Fietz T, Kohler A, Petersen V, Tesch H, Spring L, et al. Treatment and pattern of bone metastases in 1094 patients with advanced breast cancer – results from the prospective German Tumour Registry Breast Cancer cohort study. *Eur J Cancer* 2017;79:139–48.
- [141] von Moos R, Body JJ, Rider A, de Courcy J, Bhowmik D, Gatta F, et al. Bone-targeted agent treatment patterns and the impact of bone metastases on patients with advanced breast cancer in real-world practice in six European countries. *J Bone Oncol* 2018;11:1–9.
- [142] Bhowmik D, Song X, Intorcchia M, Gray S, Shi N. Examination of burden of skeletal-related events in patients naive to denosumab and intravenous bisphosphonates therapy in bone metastases from solid tumors population. *Curr Med Res Opin* 2018;1–24.
- [143] Stickeler E, Fehm T. Targeted and osteo-oncologic treatment in early breast cancer: what is state-of-the-art and what might become so within the next 5 years? *Breast Care (Basel)* 2014;9:161–7.
- [144] Croucher PJ, McDonald MM, Martin TJ. Bone metastasis: the importance of the neighbourhood. *Nat Rev Cancer* 2016;16:373–86.
- [145] Peinado H, Zhang H, Matei IR, Costa-Silva B, Hoshino A, Rodrigues G, et al. Pre-metastatic niches: organ-specific homes for metastases. *Nat Rev Cancer* 2017;17:302–17.
- [146] Gawrzak S, Rinaldi L, Gregorio S, Arenas EJ, Salvador F, Urošević J, et al. MSK1 regulates luminal cell differentiation and metastatic dormancy in ER(+) breast cancer. *Nat Cell Biol* 2018;20:211–21.
- [147] Oskarsson T, Batlle E, Massague J. Metastatic stem cells: sources, niches, and vital pathways. *Cell Stem Cell* 2014;14:306–21.
- [148] LeVasseur N, Clemons N, Hutton B, Shorr R, Jacobs C. Bone-targeted therapy use in patients with bone metastases from lung cancer: a systematic review of randomized controlled trials. *Cancer Treat Rev* 2016;50:183–93.
- [149] Bansal P, Osman D, Gan GN, Simon GR, Boucher Y. Recent advances in immunotherapy in metastatic NSCLC. *Front Oncol* 2016;6:239.
- [150] Grossmann KF, Margolin K. Long-term survival as a treatment benchmark in melanoma: latest results and clinical implications. *Ther Adv Med Oncol* 2015;7:181–91.
- [151] Francoso A, Simioni PU. Immunotherapy for the treatment of colorectal tumors: focus on approved and in-clinical-trial monoclonal antibodies. *Drug Des Devel Ther* 2017;11:177–84.
- [152] Cheng ML, Fong L. Effects of RANKL-targeted therapy in immunity and cancer. *Front Oncol* 2013;3:329.
- [153] Ahern E, Harjunpaa H, O'Donnell JS, Allen S, Dougall WC, Teng MWL, et al. RANKL blockade improves efficacy of PD1-PD-L1 blockade or dual PD1-PD-L1 and CTLA4 blockade in mouse models of cancer. *Oncoimmunology* 2018;7:e143088.
- [154] Smyth MJ, Yagita H, McArthur GA. Combination anti-CTLA-4 and anti-RANKL in metastatic melanoma. *J Clin Oncol* 2016;34:e104–6.
- [155] Liede A, Hernandez RK, Wade SW, Bo R, Nussbaum NC, Ahern E, et al. An observational study of concomitant immunotherapies and denosumab in patients with advanced melanoma or lung cancer. *Oncoimmunology* 2018;7:e1480301.
- [156] Saad F, Sternberg CN, Mulders PFA, Niepel D, Tombal BF. The role of bisphosphonates or denosumab in light of the availability of new therapies for prostate cancer. *Cancer Treat Rev* 2018;68:25–37.
- [157] Ahern E, Smyth MJ, Dougall WC, Teng MWL. Roles of the RANKL-RANK axis in

- antitumour immunity – implications for therapy. *Nat Rev Clin Oncol* 2018;15:676–93.
- [158] Coleman R. Treatment of metastatic bone disease and the emerging role of radium-223. *Semin Nucl Med* 2016;46:99–104.
- [159] Saad F, Carles J, Gillesen S, Heidenreich A, Heinrich A, Gratt J, et al. Radium-223 and concomitant therapies in patients with metastatic castration-resistant prostate cancer: an international, early access, open-label, single-arm phase 3b trial. *Lancet Oncol* 2016;17:1306–16.
- [160] 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 Oncol* 2019. Epub ahead of print.
- [161] Ortiz A, Lin SH. Osteolytic and osteoblastic bone metastases: two extremes of the same spectrum? *Recent Results Cancer Res* 2012;192:225–33.
- [162] Woolf DK, Padhani AR, Makris A. Assessing response to treatment of bone metastases from breast cancer: what should be the standard of care? *Ann Oncol* 2015;26:1048–57.
- [163] Suvannasankha A, Chirgwin JM. Role of bone-anabolic agents in the treatment of breast cancer bone metastases. *Breast Cancer Res* 2014;16:484.