

Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel

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Bisphosphonates (BP) prevent, reduce, and delay cancer-related skeletal complications in patients, and have substantially decreased the prevalence of such events since their introduction. Today, a broad range of BP with differences in potency, efficacy, dosing, and administration as well as approved indications is available. In addition, results of clinical trials investigating the efficacy of BP in cancer treatment-induced bone loss (CTIBL) have been recently published. The purpose of this paper is to review the current evidence on the use of BP in solid tumours and provide clinical recommendations. An interdisciplinary expert panel of clinical oncologists and of specialists in metabolic bone diseases assessed the widespread evidence and information on the efficacy of BP in the metastatic and nonmetastatic setting, as well as ongoing research on the adjuvant use of BP. Based on available evidence, the panel recommends amino-bisphosphonates for patients with metastatic bone disease from breast cancer and zoledronic acid for patients with other solid tumours as primary disease. Dosing of BP should follow approved indications with adjustments if necessary. While i.v. administration is most often preferable, oral administration (clodronate, IBA) may be considered for breast cancer patients who cannot or do not need to attend regular hospital care. Early-stage cancer patients at risk of developing CTIBL should be considered for preventative BP treatment. The strongest evidence in this setting is now available for ZOL. Overall, BP are well-tolerated, and most common adverse events are influenza-like syndrome, arthralgia, and when used orally, gastrointestinal symptoms. The dose of BP may need to be adapted to renal function and initial creatinine clearance calculation is mandatory according to the panel for use of any BP. Subsequent monitoring is recommended for ZOL and PAM, as described by the regulatory authority guidelines. Patients scheduled to receive BP (mainly every 3–4 weeks i.v.) should have a dental examination and be advised on appropriate measures for reducing the risk of jaw osteonecrosis. BP are well established as supportive therapy to reduce the frequency and severity of skeletal complications in patients with bone metastases from different cancers.

Key words: bisphosphonates, bone, cancer, CTIBL, metastases, SRE

Introduction

Bisphosphonates (BP) reduce and delay skeletal morbidity and the resulting complications of osteoporosis and skeletal morbidity due to metastatic bone disease (MBD). BP have therefore been used for >15 years to improve the outcome

of patients with bone metastases from solid tumours. In recent years, a wealth of publications on BP efficacy and safety was generated, providing a rationale for guidelines on the use of various BP compounds in solid tumours, particularly with respect to administration route, dose optimization, initiation, duration, and monitoring of therapy.

This paper offers clinical recommendations on the role of BP in the metastatic and nonmetastatic settings, reflecting

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consensus of an interdisciplinary expert group based on a concise review of available evidence. The recommendations were drafted at a consensus meeting followed by reviews of manuscript drafts circulated within the panel. These recommendations should be understood as an auxiliary tool for supporting and informing individual clinicians' decisions regarding choice and implementation of BP therapy in patients with solid tumours.

BP effectively inhibit osteoclast-mediated bone resorption [1], thus providing the rationale for their use for skeletal protection in osteoporosis [2] as well as in various stages in the natural history of solid tumours [1]. BP compounds are remarkably variable in structure and resulting physicochemical and biological properties [1], including potency [3]. The newer, nitrogen-containing bisphosphonates (N-BP) such as ibandronate (IBA), pamidronate (PAM), risedronate (RIS), and zoledronic acid (ZOL) are several orders of magnitude more potent than earlier generation BP such as etidronate, tiludronate and clodronate (CLO). While non-N-BP are incorporated into adenosine triphosphate (ATP)-containing compounds, thus inhibiting cell function [4], N-BP interfere with cell signalling and block the prenylation of small signalling proteins (e.g. Ras, Rho) which are essential for cell function and survival [5, 6]. Farnesyl pyrophosphate synthase was proposed as main enzymic target of N-BP [5]; however, more recent reports indicate that the main biological activity of N-BP is directed against protein geranylgeranylation [6]. Non-N-BP induce production of a unique ATP analogue that can directly induce apoptosis [3]. The variability in structure and potency (Figure 1 as electronic supplement) has substantial biological and clinical implications [1].

MBD is commonly seen with various cancer types, including frequent ones such as those of the breast and prostate. Accordingly, bone metastases affect a multitude of patients with advanced disease (e.g. >60% of patients with metastatic breast cancer [7]). They often lead to skeletal complications, such as pain, pathological fractures requiring surgery and/or radiation to bone, spinal cord compression, or hypercalcaemia of malignancy [8–10], many of which are associated with life-

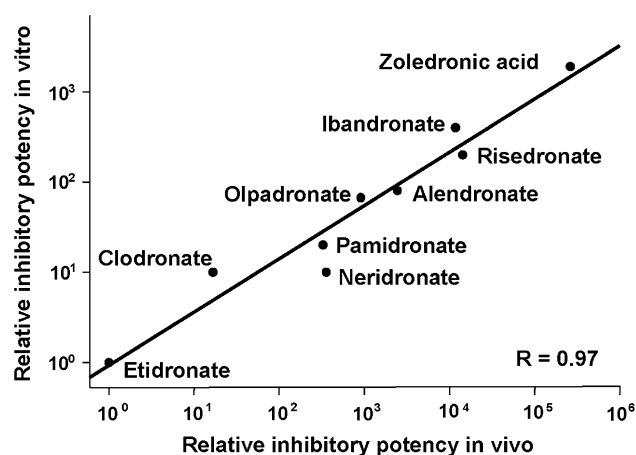


Figure 1. *In vivo* potency of bisphosphonates correlates with *in vitro* potency. Differences in structure of the bisphosphonates have strong influence on the potency.

altering morbidity and can negatively impact survival times. Pathologic fractures are the most common skeletal events, reflecting the fragility of patients' bones and the burden of bone pain. Many patients will have to receive radiation to bone as treatment for bone pain and in order to prevent complications. Moreover, skeletal events are associated with a loss of mobility and social functioning, a decrease in quality of life (QoL) [11–13], and with a substantial increase in medical costs [14].

To date, BP are the key treatment option for reducing, delaying and preventing skeletal complications associated with bone metastases, thus maintaining and restoring patient's mobility and function and reducing pain [15]. Health economic studies on BP indicate that they are a cost-effective treatment considering drug costs, QoL benefits (especially due to bone pain reduction), and incidence and costs of skeletal complications [16–18]. The choice of BP for a given clinical setting should be evidence based.

In nonmetastatic, early-stage cancer, BP were shown in clinical trials to be effective in preventing cancer treatment-induced bone loss (CTIBL) due to hormone deprivation therapy [19–21]. Moreover, some evidence that they may prevent bone metastasis [22, 23] has resulted in a large trial program investigating this hypothesis.

It is finally recommended to consider the use of calcium (1 g/day) and vitamin D₃ (800 IU/day) whenever BP are used.

use of BP in metastatic cancer

The skeleton is the preferred site of metastasis for many solid tumours. Across different solid tumour types the prevalence of MBD is highest in breast and prostate cancer (65%–75%) followed by thyroid (60%), lung (40%), and bladder cancer (30%–40%) [24]. As malignant bone lesions are characterized by a disordered bone metabolism, all patients with MBD are at risk of developing skeletal complications (Table 1). Skeletal complications are also associated with increased mortality [25]. Therefore, patients with MBD, irrespective of the cancer type, are in need of and should be considered for a therapy that effectively inhibits bone resorption. BP, mostly compared with placebo, have been proven to reduce and delay the occurrence of skeletal events [7] and control bone pain in patients with MBD [15, 26–28], thereby preserving mobility, social functioning, and QoL over the course of progressive metastatic disease [12, 13, 28]. BP efficacy has been quantified using various definitions of skeletal complications, measures, and methods for statistical analysis (Table 1). Moreover, sample size may influence the statistical significance of the outcome. This should be borne in mind when interpreting trial data.

breast cancer

Nearly 70% of breast cancer patients treated with placebo in controlled BP trials experience more than one skeletal-related event (SRE), and ~50% have a pathological fracture >2-year period [29]. Experience of a pathological fracture increases the risk of death in breast cancer patients by 32% [25]. Several clinical trials using different measures of SRE as a composite

Table 1. Measuring therapeutic benefit of bisphosphonates in patients with bone metastasis

Goal of therapy	Relevant end point
Prevent skeletal complications/bone events ^a	Percent of patients with ≥1 event
Delay onset of skeletal complications	Time to first event
Reduce the rate of occurrence of complications	SMR or SMPR ^b
Reduce the number of complications and/or delay the time to the first and subsequent complications, thereby reducing overall skeletal morbidity	Multiple event analyses ^c

^aDefinition of skeletal complications/bone events for different bisphosphonates to assess the efficacy: clodronate: Fractures, radiotherapy, hypercalcaemia of malignancies; pamidronate/zoledronic acid: fractures, surgery to bone, radiation to bone, spinal cord compression, HCM; IBA: fractures, radiation to bone, surgery to bone.

^bSMR (events per year) or SMPR (number of 12-week periods on which a patient experiences new bone event divided by the number of periods on study) assess the number of events that occur during a defined time period.

^cIn contrast to the analysis of the proportion of patients with ≥1 skeletal events or the time to first event, which ignore all events after the first one, or skeletal morbidity (period) rates which fail to consider the timing of events, multiple event analyses are statistically robust methods accounting for all skeletal events and for the timing of events throughout the course of disease. The result is expressed as a hazard ratio indicating the reduction in the risk of skeletal events compared with control.

SMR, skeletal morbidity rate; SMPR, skeletal morbidity period rate.

end point have shown the benefits of BP to patients with advanced breast cancer (Table 2) [38]. Currently, four BP are approved for the treatment of MBD in breast cancer: oral CLO, oral or i.v. IBA, i.v. PAM, and i.v. ZOL. Meta-analysis of eight trials including women with advanced breast cancer and existing bone metastasis showed a 17% reduction in the risk of developing a skeletal event for patients on BP therapy [37]. Together with PAM, ZOL is the only i.v. BP demonstrating a statistically significant clinical benefit across multiple end points [26, 30, 36, 39]. The only head-to-head comparison of two BP in an appropriately powered phase III study was between ZOL and PAM [36]. In this study, the proportion of patients with at least one SRE was similar for ZOL and PAM; however, ZOL reduces the overall risk of developing any skeletal complications by 20% when compared with PAM [relative risk (RR) = 0.799; *P* = 0.025] [36, 40, 41]. In the subset of patients with lytic bone lesions, the greater efficacy of ZOL over PAM was demonstrated [41]. The efficacy of BP against bone pain was investigated by several trials and is shown for pooled studies of oral IBA (*P* = 0.001), i.v. IBA (*P* = 0.0006), oral CLO (*P* = 0.01), and PAM (*P* < 0.001) [15]. In a prospective placebo-controlled study, ZOL consistently reduced brief pain inventory composite pain scores at each evaluation carried out throughout a 12-month period (*P* < 0.05) [26]. Moreover, it has shown that oral IBA and i.v. ZOL can reduce bone turnover markers [42]; however current evidence does not support the use of bone markers as basis for clinical decision making.

On the grounds of efficacy data (which are difficult to interpret due to the lack of a multiple event analysis and suboptimal compliance) [33, 43], the panel recommends to offer an N-BP to breast cancer patients with MBD.

prostate cancer

Prostate cancer commonly metastasizes to bone; this can lead to significant skeletal morbidity. Although BP are known to reduce excessive bone turnover while preserving bone structure and mineralization in patients with breast cancer, in prostate cancer efficacy data differ (Table 3). ZOL significantly reduced the incidence of SREs by 36% [hazard ratio (HR) = 0.640; *P* = 0.002] and delayed the first SRE by >5 months (*P* = 0.009) [52] compared with placebo. ZOL also provided significant long-term reductions in bone pain compared with placebo [53].

In contrast, several randomized, placebo-controlled trials of early generation BP (etidronate (ETI), CLO, PAM) showed no statistically significant clinical benefit in patients with bone metastases from prostate cancer. Although results indicative of benefit were reported (Table 3), neither oral nor i.v. CLO showed statistically significant pain relief [45, 46, 55] or any significant improvement of symptomatic bone progression-free survival (*P* = 0.066) [46]. Also, PAM failed to demonstrate a significant overall treatment benefit compared with placebo in palliation of bone pain, improvement of QoL, or reduction of SREs [51] in patients with bone pain and disease progression after first-line hormonal therapy. In a small open-label, nonrandomized study (*n* = 25), i.v. IBA was shown to be effective for reducing pain from prostate cancer metastasized to bone [49]; efficacy in terms of reduction of skeletal events was not measured.

Based on the available evidence demonstrating a significantly lower incidence of skeletal complications as well as durable pain palliation, the opinion of the panel is that ZOL is presently the BP treatment of choice for patients with hormone refractory prostate cancer metastatic to bone. And it has been published that SRE reduction is greatest in patients without pain, thus patients should probably not have to wait for symptoms before starting ZOL therapy in this setting [56, 57].

lung cancer

ZOL reduced the risk of developing an SRE by 31% (HR = 0.693, *P* = 0.003) in a double-blind, placebo-controlled, 21-month trial that included 773 patients with lung cancer and other solid tumours (except breast and prostate; 244 with non-small-cell lung cancer (NSCLC) and 36 with small-cell lung cancer) [58, 59]. Therefore, the panel recommends that lung cancer patients with bone metastases and a reasonable chance of benefiting (i.e. expected survival times, patients performance status, etc.) should be considered for ZOL treatment. Further prospective clinical trials are warranted to better define the role of BP in the treatment strategy of NSCLC, with particular emphasis on locally advanced stage IIIB disease after completion of chemo/radiotherapy.

Table 2. Overview of the breast cancer trials with BP

BP	Study	N	Dose	Design and control	1 end point	Relative risk of skeletal events RR (95% confidence interval)
i.v. IBA	Body <i>et al.</i> [30]	462	2 or 6 mg	<ul style="list-style-type: none"> • Double blind • Placebo • Monthly, up to 2 years 	SMPR	0.82 (0.67, 1.00)
p.o. IBA	Body <i>et al.</i> [31]	564	50 mg	<ul style="list-style-type: none"> • Double blind • Placebo • Daily, up to 96 weeks 	SMPR	0.86 (0.73, 1.02)
p.o. CLO	Kristensen <i>et al.</i> [32]	100	1600 mg	<ul style="list-style-type: none"> • Randomized • Open label • Controlled • Daily, for 2 years 	Number of skeletal events	0.69 (0.40, 1.20)
p.o. CLO	Paterson <i>et al.</i> [33]	185	1600 mg	<ul style="list-style-type: none"> • Double blind • Placebo • Daily for 3 years 	Combined rate of morbid skeletal events	0.83 (0.68, 1.02)
p.o. CLO	Tubiana-Hulin <i>et al.</i> [34]	144	1600 mg	<ul style="list-style-type: none"> • Randomized • Double blind • Controlled • Daily, up to 1 year 	New bone event	0.92 (0.92, 1.19)
i.v. PAM	Hortobagyi <i>et al.</i> [29] Theriault <i>et al.</i> [35]	754	90 mg	<ul style="list-style-type: none"> • Randomized • Double blind • Placebo • Every 3–4 weeks, up to 24 cycles 	Skeletal morbidity rate (events/per year)	0.77 (0.69, 0.87) ^a
i.v. ZOL	Kohno <i>et al.</i> [26]	228	4 mg	<ul style="list-style-type: none"> • Randomized • Double blind • Placebo • Every 4 weeks, for 1 year 	SRE rate ratio	0.59 (0.42, 0.82)
i.v. ZOL	Rosen <i>et al.</i> [36]	412 ^b	4 mg	<ul style="list-style-type: none"> • Randomized • Double blind • PAM • Every 4 weeks, for 2 year 	Proportion of patients who experienced ≥1 SRE	0.80 (0.66, 0.97) [36]

Trials investigating the effect of bisphosphonates at currently recommended doses on the overall risk of skeletal events in patients with advanced breast cancer [37]. Primary end points were achieved in all trials; for better comparability, hazard ratios are indicated according to the Cochrane review paper [37]. The value of such comparisons is, however, limited by marked heterogeneity in patient populations and study characteristics.

^aCombined analysis of Aredia studies 18 and 19 [37].

^bPatients (with bone lesions secondary to advanced breast carcinoma) that entered extension study.

BP, bisphosphonates; IBA, ibandronate; PAM, pamidronate; ZOL, zoledronic acid; CLO, clodronate; SRE, skeletal-related event; RR, relative risk.

renal cell carcinoma and other solid tumours

Renal cell cancer with lymph node metastases at primary diagnosis often metastasizes to bone and patients are at high risk of skeletal complications [60]. In 46 patients, ZOL reduced the risk of having a SRE by 58% (HR = 0.418; $P = 0.010$) and the incidence of SREs by 41% (HR = 0.590; $P = 0.011$). Occurrence of the first SRE was delayed by ~1 year (424 days versus 72 days in the placebo group, $P = 0.007$) [58, 59].

ZOL is the only BP with data on reduction of SREs in other tumour types, such as thyroid cancer ($n = 6$),

bladder cancer ($n = 26$), and 16 further types of solid tumours ($n = 143$) [58, 59]. In the subset 'other tumours', ZOL reduced the proportion of patients with SRE (33% versus 43%) and extended the median time to first SRE to 314 days compared with 168 in the placebo arm. Both outcomes did not reach statistical significance ($P = 0.11$ and $P = 0.051$, respectively) [59]. Some tolerability data have been reported for i.v. IBA in colorectal carcinoma [61], and a further study in different tumour types ($n = 66$) has shown decreased analgesic requirement for patients with CLO treatment [62].

The panel recommends that ZOL should be considered in all patients with bone metastases from renal cell carcinoma and

Table 3. Overview of the prostate cancer trials with BP

BP	Author	N	Dose	Design	1 end point	Results related to pain or skeletal events [44] RR (95% confidence interval)
CLO	Elomaa <i>et al.</i> [45]	75	3.2 g/day (1st month) 1.6 g/day (p.o.)	<ul style="list-style-type: none"> • Randomized 	Pain relief	Proportion of patients with pain response 0.47 (0.15, 1.47)
CLO	Dearnaley <i>et al.</i> [46] ^a	311	2080 mg/day (p.o.)	<ul style="list-style-type: none"> • 3-year trial • Randomized • Double blind placebo controlled 	Symptomatic BPFs	Proportion of patients with any skeletal event 0.79 (0.50, 1.26)
CLO	Ernst <i>et al.</i> [47]	204	1500 mg/3 weeks (i.v.)	<ul style="list-style-type: none"> • Randomized 	Palliative response	Proportion of patients with pain response 0.75 (0.42, 1.36)
ETI	Smith [48]	57	200 mg b.i.d.	<ul style="list-style-type: none"> • Randomized • Double blind • Placebo controlled 	Pain relief	Proportion of patients with pain response 0.73 (0.14, 4.00)
IBA	Heidenreich [49, 50]	25	6 mg/4 weeks (i.v.)	<ul style="list-style-type: none"> • Open • Prospective • Nonrandomized 	Visual analog pain score	Significant pain reduction ($P < 0.001$)
PAM	Small <i>et al.</i> [51]	378	90 mg/3 weeks (i.v.)	<ul style="list-style-type: none"> • 27-week trial • Randomized • Double blind • Placebo controlled 	BPI	Proportion of patients with any skeletal event 0.98 (0.61, 1.58) Proportion with pathological fractures 1.26 (0.68, 2.32) Change in average BPI score after 9 weeks -0.61 (PAM) versus 0.44 (placebo); $P = 0.46$
ZOL	Saad [52–54]	643	4 mg/3 weeks	<ul style="list-style-type: none"> • 24-month trial (15-months core phase, 9-months extension) • Randomized • Double blind • Placebo controlled 	Percentage of patients with >1 SRE	Proportion of patients with any skeletal event 0.71 (0.50, 0.99) Proportion with pathological fractures 0.57 (0.38, 0.88)

Trials investigating the effect of bisphosphonates at currently recommended doses on the outcome measures related to pain or skeletal events in patients with hormone refractory prostate cancer (^acommencing or responding to hormone therapy) [44]. A study on i.v. IBA indicating a significant pain reduction [49, 50] was not included in the Cochrane review since it was a nonrandomized study. Palliative response (present pain intensity minus 2 points or analgesic intake reduced by 50%).

BP, bisphosphonates; RR, relative risk; CLO, clodronate; BPFs, bone progression-free survival; ETI, etidronate; IBA, ibandronate; PAM, pamidronate; BPI, brief pain inventory; ZOL, zoledronic acid; SRE, skeletal-related event.

other solid tumours as discussed above, based on an assessment of their expected survival time and an expectation of overall palliative benefit.

choice of administration route

Oral administration (CLO, IBA) is approved in patients with breast cancer, and should be considered for patients who cannot

or do not need to attend regular hospital care. Oral administration requires precautionary measures to ensure absorption and—for some BP—to avoid gastrointestinal (GI) adverse event (AE) [63, 64]. The inconvenience and complexity of oral dosing requirements, the potential for adverse effects, especially when dosing recommendations are not followed, and very low absorption rates of oral BP even under ideal conditions, may contribute to poor outcomes [65].

Generally, i.v. administration (CLO, IBA, PAM, and ZOL) is preferable since it can help ensuring adherence and persistence compared with oral administration and can be combined with infusions of nonnephrotoxic chemotherapy or clinical monitoring of metastatic patients. Although i.v. administration is usually done in an outpatient clinic setting, delivery at the patient's home has been evaluated [13] and can be considered. Infusion time ranges from 15 min (ZOL, IBA) up to 2 h (PAM).

adherence to and persistence with BP therapy

Oral BP require regular intake, must be taken on an empty stomach and—in case of IBA—in an upright position. Therefore, all patients receiving oral BP need to be educated about the pivotal importance of adherence to and persistence with therapy. Both are known to be poor in patients self-administering oral BP for osteoporosis [66, 67], even with patient support [68], particularly with weekly or daily dosing [2, 66]. In the metastatic setting, there are also reports of low persistence [69, 70] that can be expected to jeopardize therapeutic efficacy. In a study assessing patient preference for either ZOL or PAM, 92% preferred ZOL because shorter infusions caused less disruption to their daily schedule [71]. Compliance with CLO in the adjuvant and metastatic setting has been reported to be acceptable [22].

initiation, dosing and duration of BP therapy in metastatic cancer

There is a paucity of data for optimal use of BP, mainly regarding initiation and treatment duration. To maximize the benefit of BP treatment, the panel recommended—in the absence of data—considering the start of therapy as soon as bone metastases are diagnosed by radiographic techniques, even if they are asymptomatic.

Dosing regimens of BP therapy for patients with bone metastases should follow the evidence generated in clinical studies. In patients with mild to moderate renal impairment [creatinine clearance (CrCl) 30–60 ml/min], regulations recommend lower doses of CLO and ZOL and longer infusion times for PAM, respectively [63, 64, 72, 73]. A recent label of IBA approved by European regulatory authorities allows a dosing regimen of 6 mg >60 min instead of 15 min when CrCl is 30–50 ml/min [74].

In patients with evidence of renal deterioration during treatment, i.v. BP should be withheld and only resumed when serum creatinine returns to within 10% of baseline [72]. However, in case of persistent renal deterioration, the panel agreed that either dose reduction or longer infusion time could be considered under close monitoring when clinical assessment indicates that BP therapy should not be discontinued. Because of the importance of continuing BP treatment to prevent further SREs, discontinuation of therapy should be limited to patients who cannot tolerate BP therapy.

Treatment with ZOL is contraindicated in patients with severe renal dysfunction (serum creatinine >265 $\mu\text{mol/l}$ >3.0 mg/dl, CrCl <30 ml/min). In such cases, a reduced dose of 2 mg i.v. IBA >60 min can be used in patients with breast cancer, while there are no data for other tumours. Treatment with CLO is contraindicated in patients with CrCl <10 ml/min or serum creatinine >440 $\mu\text{mol/l}$.

Benefit of BP therapy with ZOL and IBA in breast cancer has been shown for a treatment duration of up to 2 years [36, 52, 59, 75]. Since the risk of SREs is going to continue, the expert panel—in the absence of supporting data—recommends continuation of therapy beyond 2 years but always based on an individual risk assessment. Specifically, it should not be discontinued once skeletal events occur, as controlled studies with ZOL show a significant reduction in the risk of subsequent skeletal events [52, 76]. In case of disease progression, the anticancer treatment should be adapted according to the patient's clinical situation. In patients with disease progression in the skeleton and pain despite the use of oral BP or PAM, change to ZOL or IBA can improve pain control [77, 78].

use of bone markers in BP therapy

The use of bone markers for adjusting BP therapy and for the prediction of patients' risk of bone metastasis is under investigation with ZOL (BISMARCK, OPTIMIZE). There is no prospective trial at this point which shows that bone markers are reliable for individual patients: they are only valid for a cohort of patients in respective studies. Currently, the panel does not recommend the use of bone markers in clinical routine [42, 79, 80, 81].

elderly patients

There are no specific limitations for the use of BP in the elderly. An International Society of Geriatric Oncology task force reviewed information from the literature on BP in elderly patients with bone metastases. They recommended that CrCl (because serum creatinine values can be misleading in the elderly) should be monitored in every patient, and an agent with best possible renal tolerability should be used where evidence of similar efficacy is available. The assessment and optimization of hydration status was recommended in this often dehydrated population [82].

managing QoL with BP

One goal of BP therapy in metastatic cancer is to keep patients functional and mobile for as long as possible, thus preserving their QoL and delaying its deterioration. Reduction and postponement of skeletal complications and the associated life-altering morbidity is essential for this purpose [11, 12, 83–86]. New tools for measuring QoL in routine practice are being developed and need to be validated in different countries.

pain control and BP

Adequate pain control is a key aspect of QoL maintenance in patients with bone metastases. Analgesic therapy should follow

a stepwise escalation regimen as per World Health Organization guidelines [87]. Along with analgesics, BP therapy is a major factor contributing to the preservation of QoL in patients with progressive metastatic disease [11, 12, 28, 31, 50, 83, 88–92]. Controlled clinical studies have shown BP therapy, apart from its benefits in terms of skeletal morbidity, to reduce bone pain including opioid-resistant pain, and over the course of progressive disease to maintain it at lower levels compared with controls [15].

concomitant BP therapy given with anticancer therapy

A growing body of preclinical evidence from *in vitro* studies and animal models demonstrates that BP can reduce skeletal tumour burden and prevent metastasis to bone [93]. N-BP have been shown to exert anti-tumour effects *in vitro* through apoptosis induction and several other mechanisms [3, 94]. ZOL inhibits tumour cell adhesion to the extracellular matrix, invasion, and angiogenesis [3]. IBA prevented adhesion and spreading of tumour cells to bone and tumour cell invasion. These inhibitory effects were additive when IBA was given with paclitaxel or docetaxel. In animal models of tumour-induced osteolysis, IBA significantly reduced the development of osteolytic lesions [94]. ZOL and IBA were also shown to exert synergistic antitumour activity when combined with various other anticancer agents [95–99], with some evidence for higher *in vitro* efficacy with ZOL [99].

These preliminary data indicate that N-BP might have clinical antitumour effects by themselves or in combination with other anticancer treatments such as chemotherapy, hormone therapy, radiotherapy [100, 101], or monoclonal antibodies. However, special caution should be exerted when administering cytotoxic drugs that can be nephrotoxic, such as platinum salts, some antibiotics, and nonsteroidal anti-inflammatory drugs (NSAIDs). The panel indicated that nephrotoxic chemotherapy should not be administered on the same day as an i.v. BP to reduce the risk of renal toxicity.

AE associated with BP therapy for metastatic cancer

BP therapy for metastatic cancer is generally well tolerated, with a low rate of (AE) in clinical practice [102]. Patients should be instructed to recognize and report signs and symptoms indicating key AE, and both the occurrence and severity of AE should be monitored at each visit. Monitoring must include questioning for AE and appropriate evaluation of CrCl in patients receiving i.v. BP.

AE commonly associated with BP are generally manageable. Side-effects related to BP pharmacology include osteomalacia and (an AE associated with 1st generation but not observed with 2nd or 3rd generation BP) hypocalcaemia. AE unrelated to the anti-resorptive effect of BP include acute-phase reactions, GI problems, local reactions at the injection site, and more rarely nephrotoxicity and uveitis. Osteonecrosis of the jaw (ONJ) has been described in recent years in association with the use of BP.

‘Hypocalcaemia’ is typically observed in conditions of high bone turnover, such as in mixed or sclerotic lesions. Clinically relevant hypocalcaemia is very rarely observed and may be prevented with calcium and vitamin D₃ from the start of therapy. A transient increase in ‘bone pain’ is seen mostly in patients with painful bone lesions associated with aggressive bone resorption treated with i.v. BP; it is usually mild and transient and can be managed with preventive or therapeutic analgesics. Transient ‘acute-phase reactions’ characterized by fever and myalgia occurs in 15%–30% of patients [103], generally after the first infusion of an N-BP, less frequently after the following infusions. They peak within 24–48 h and subside after ~3 days [104]. They are no reason for treatment discontinuation and can be managed with preventive or therapeutic analgesics (e.g. paracetamol or ibuprofen (expert consensus, despite of this being an NSAID)).

‘Nephrotoxicity’ characterized by elevation of serum creatinine level and potentially acute tubular necrosis with reversible or irreversible kidney damage may occur in patients receiving i.v. BP [105]. Grade 3 creatinine elevations have been observed in three (3.3%) of prostate cancer patients treated with 4 mg ZOL and in one (1.3%) receiving a placebo [54]. Renal effects are generally seen after rapid infusion leading to high BP concentrations in the blood and kidney. Medline reports on creatinine elevation were more frequent with ETI or CLO (8% and 5%, respectively) than with PAM (2%), alendronate (0%), or IBA (<1%) [106], the difference reaching statistical significance for ETI only. No significant difference in renal tolerability was seen in a pair wise comparison of PAM (90 mg i.v. >2 h) and ZOL (4 mg i.v. >15 min) in a large clinical trial in breast cancer [36]. ZOL can be safely administered with proper serum CrCl evaluation, in cancer patients previously treated with i.v. BP [107]. In a phase III trial of patients with MBD from breast cancer, 6 mg IBA infused >1–2 h had a renal safety profile comparable to that of placebo [108, 109]. Manufacturers’ recommendations for infusion times [63, 64, 72, 73] should be followed to minimize the potential for renal AE since C_{max} determines the nephrotoxicity of BP. To avoid renal toxicity with i.v. BP, patients need to be adequately hydrated before treatment, and monitoring of serum creatinine is recommended [110].

GI problems with oral BP include mild gastric irritation, erosions, and diarrhoea, and rarely ulcers, perforations, and strictures. The more severe GI AE are uncommon with weekly dosing regimens. Patients should be instructed to comply well with the dosage prescriptions [fasting ≥1–2 h before and ≥1 h after intake (except water), in the case of oral IBA upright position for ≥1 h after intake] [63, 64]. Local reactions at the injection site include phlebitis, pain, local swelling, and ulceration. ‘Uveitis’ is rare and usually resolves within 1–2 weeks of treatment cessation.

ONJ is an uncommon but potentially serious complication predominantly seen in patients receiving potent i.v. N-BP [111] including PAM, ZOL [112, 113] and IBA [114], observed mostly during treatment for multiple myeloma or breast cancer [102, 111]. ONJ was also seen in a few patients treated with oral alendronate and RIS for osteoporosis or Paget’s disease [112, 115, 116], and was recently reported in one multiple myeloma patient treated with CLO [117]. The aetiology of ONJ is

unclear but likely multifactorial [116]. Actinomyces has been found frequently in these lesions [118], indicating that osteomyelitis at sites of dental/jaw trauma may contribute to the condition. There is a strong association with dental pathology and interventions [102, 111, 112, 119, 120]. At least 60% of cases occur after dentoalveolar surgery to treat infection, and the remainder often involves patients with dentures [111]. The risk of experiencing ONJ seems to be time- and dose dependent [111]. Other potential risk factors include chemotherapy [114], glucocorticosteroids [102], and thalidomide [102].

Best practices for identifying, staging and managing ONJ in oncology patients on i.v. N-BP have been proposed [111, 116]. Preventive strategies aim at avoiding dental infection and dentoalveolar surgery. Before starting i.v. N-BP treatment, patients should have a dental examination and any treatment required [116]. They must be advised to keep good oral hygiene, have active oral infections treated, and sites at high risk for infection eliminated. Patients with dental problems other than ONJ should get the least invasive dental treatment. Until healing of invasive dental surgery, temporary discontinuation of BP therapy may be considered [116], although there are no data available on which to make a firm recommendation and the decision to stop or continue should be made on a case by case basis.

prevention of CTIBL

Patients receiving adjuvant anticancer treatment are at significant risk of CTIBL, including osteopenia and osteoporosis. Cytotoxic chemotherapy (CT) and hormone deprivation therapies can directly affect bone mineral density (BMD) and micro-architectural structure [121–127]. Aromatase inhibitors (AIs) or gonadotropin-releasing hormone agonists used in patients with breast or prostate cancer may result in a two- to 10-fold higher yearly bone loss compared with a healthy age-matched population [128–130]. Accelerated bone loss increases fracture risk and has long-term implications for QoL, costs, and even survival [131, 132]. Starting adjuvant endocrine therapy of early breast cancer with tamoxifen and switching to an AI after 2–3 years does not prevent a significant increase in fractures in spite of prior bone protective effect of tamoxifen [126].

In premenopausal women with CT-induced estrogen depletion and antiestrogen therapy, CLO and RIS, respectively, reduced bone loss significantly compared with placebo [133–135]. PAM stabilized bone loss in androgen-deprived patients with prostate cancer [130]. Alendronate is approved for the treatment of osteoporosis in men and 70 mg once weekly significantly increased bone mass at the spine and the total hip in men with nonmetastatic prostate cancer on androgen deprivation therapy [136]. To date, ZOL is the most intensively investigated BP in this setting and long-term data in CTIBL in large ongoing trials accruing several thousand patients in total [22, 137–139] have shown ZOL to prevent or slow bone loss during adjuvant endocrine therapy. In premenopausal patients treated with anastrozole and goserelin, ZOL prevented bone loss in lumbar spine and hip, regardless of endocrine therapy ($P < 0.0001$) [19]. When added to adjuvant letrozole in

postmenopausal patients, ZOL (4 mg every 6 months) was most effective when initiated before osteoporosis or fractures occur [3.3%, 95% confidence interval (CI) 2.8% to 3.8%; $P < 0.0001$] [20, 21]. Patients treated with delayed ZOL (i.e. after a fracture or a T-score less than -2) experienced a reduction in spine and hip BMD [139]. Similarly, in nonmetastatic prostate cancer, ZOL (4 mg every 3 months or once a year [140]) increased BMD in the spine in the first year of androgen deprivation therapy, whereas BMD decreased in patients receiving placebo (7.8%, 95% CI 5.6% to 10.0%; $P < 0.001$) [141]. Prevention of bone loss has also been demonstrated with long-term (2–3 years) CLO therapy in the adjuvant setting [135, 142, 143]. These results are of particular importance in patients who are osteopenic at baseline.

The combination of ZOL with hormone deprivation therapy is well tolerated. No cases of ONJ were so far reported, and renal function was not affected in this otherwise healthy patient population [19, 21]. In a double-blind, placebo-controlled trial in osteopenic breast cancer patients on anastrozole, IBA 150 mg orally once a month resulted in significant increase in BMD at the hip and lumbar spine ($P < 0.001$) [144].

The panel recommends that patients at risk of developing cancer treatment-induced osteopenia or osteoporosis should receive vitamin D₃ and calcium supplements. The use of BP should be considered in patients presenting risk factors related either to their BMD or other considerations described below.

These risk factors include aromatase inhibitors, T-score ≤ -1.5 , age >65 , corticosteroid use of >6 months, family history of hip fracture or history of personal fragility fracture after age 50 [145]. Patients should preferably receive a BMD test (dual energy X-ray absorptiometry (DXA)). Where no BMD test is available their risk is evaluated considering the risk factors as following: a patient with 2 or more of them should be considered for ZOL therapy supplemented with vitamin D₃ and calcium; similar considerations apply to patients with a T-score less than -2.0 or a T-score less than -1.5 plus one other risk factor [145].

future uses of BP

Three clinical trials investigating CLO as adjuvant therapy have been reported, and two indicate that BP may prevent bone metastasis [22, 146–148]. Two studies, one open-label study from Germany [146] and a randomised double-blind placebo-controlled trial from Canada, Norway, Finland, and UK [22] reported improved overall survival while a third, open-label study from Finland [147, 149] showed no effect on overall survival and initially reported a reduced disease-free survival and an increase in extra-skeletal metastases with CLO [147]. Marked imbalance in patient characteristics in the two groups weakens, however, the findings of that particular study. In the German study, a significant reduction of bone metastasis after 3 years median follow-up was no longer significant after 8.6 years [150], yet survival in the CLO arm was 80% compared with 58% in the placebo arm ($P = 0.049$), indicating a lasting overall survival gain from adjuvant CLO [22]. Recently, a meta-analysis carried out in patients with early and advanced breast cancer found no evidence of a statistically significant survival benefit in

patients receiving CLO therapy [151]. Although these results with CLO have not led to the registration with an indication for use in the setting of adjuvant breast cancer treatment, they indicate that BP may play a role in preventing bone metastasis with optimized treatment schedules or choice of drug. This is supported by the results of pilot studies [152, 153], one of which reported adjuvant ZOL to increase 12-month bone metastasis-free survival in aggressive solid tumors [152].

A large trial program (ABCSG-12, NSABP-B-34, AZURE, S0307, SUCCESS; total accrual ~18 000 patients) is further exploring the use of BP as adjuvant therapy in patients with breast cancer. The first safety analyses of the AZURE trial in 3360 patients indicate that the combination of adjuvant chemotherapy and ZOL is well tolerated, with no significant difference in the profile or severity of AE between groups [154]. NSABP-B-34 is a placebo-controlled phase III trial of adjuvant CLO for the prevention of bone metastases in patients with operable breast cancer. Accrual of 3323 patients was completed in 2004 and results are expected for 2009. S0307 is a randomized phase III head-to-head comparison of i.v. ZOL acid with oral IBA or CLO for the prevention of bone metastases in women with early breast cancer. Primary end point is disease-free survival and target accrual is 6000 patients. ABCSG-12 is a prospective randomized trial comparing preventative ZOL use without BP treatment in premenopausal patients with endocrine-responsive breast cancer who receive goserelin + tamoxifen/anastrozole. Accrual of 1801 patients was finalized in 2006, and event-free survival is the primary end point. The German trial SUCCESS (primary end point disease-free survival) has recently completed the enrolment of 3700 early high-risk BC patients, receiving ZOL for 2 or 5 years following adjuvant chemotherapy.

Additional five randomized trials are ongoing to investigate the potential of ZOL to prevent bone metastasis in prostate and lung cancer. Mainly important are the ZEUS trial in prostate with completed enrolment (1420 patients), comparing 4 year-ZOL versus observation, and the 2419 trial run in stage IIIA–IIIB NSCLC patients, comparing 24-month-ZOL versus observation.

Pending the results from one or more of the definitive studies listed above, the panel does not recommend the use of adjuvant BP to prevent metastases.

summary of panel recommendations

- In breast cancer, an N-BP is preferably offered to patients with MBD. Generally, i.v. administration is preferable; however, oral administration should be considered for patients who cannot or do not have to attend regular hospital care.
- For patients with hormone refractory prostate cancer, ZOL therapy should be considered for preventing skeletal morbidity and improving QoL, based on evidence.
- Patients with lung, renal cell or solid tumours other than breast or prostate metastasizing to bone, ZOL therapy should be considered based on assessment of their general medical condition and expected survival time.
- BP therapy is a major factor contributing to control of pain due to MBD.

- Patients at risk of developing chemotherapy or hormone-deprivation therapy-induced or hormone deprivation therapy-induced (e.g. by AI or ADT) osteopenia or osteoporosis should be considered for preventative BP therapy. Presently the strongest evidence is in favour of ZOL.
- Dosing regimens of BP therapy should follow the scientific data and respective regulatory recommendations and adjustments due to preexisting medical conditions.
- Since the risk of SREs is continuous, the expert panel recommends continuing treatment until 2 years, even if a patient experiences a bone event. Continuation of therapy beyond 2 years based on an individual risk assessment is recommended.
- Transient acute-phase reactions are no reason for treatment discontinuation and can be managed with preventative or therapeutic analgesics (e.g. paracetamol or ibuprofen).
- In patients with renal impairment receiving i.v. BP, lower doses, longer infusion times, and selecting a BP with best possible renal tolerability (e.g. IBA) is recommended.
- To avoid renal toxicity with i.v. BP, patients should be adequately hydrated before treatment, and appropriate monitoring of serum creatinine is recommended.
- Calcium and vitamin D₃ should be considered from the start of therapy with BP.
- In case of oral administration, patients need to be instructed to comply well with the dosage prescriptions to prevent GI problems and maintain the adherence to therapy.
- Before starting N-BP treatment, patients should have a dental examination and appropriate treatment and should be advised to maintain good oral hygiene.
- For each patient with ONJ, an individual benefit/risk evaluation should be carried out to assess continuation or temporary discontinuation of BP therapy.

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This guidance reflects the consensus opinion of the authors. The consensus process has been initiated with a full day meeting that resulted in the formulation of core statements on all topics covered in the above described recommendations. In several rounds of revisions supported by a science agency, all panelists were asked for input on any proposed rewording. At the final draft stage, this paper has been submitted for comments to the producers of the four BP approved in oncology: Bayer Schering, Novartis, and Roche, who were asked to verify the factual statements and references for completeness, while the interpretation thereof was not to be discussed and remained entirely in the hands of the panellists. This article is dedicated to the memory of H. Fleisch.

references

1. Fleisch H. Development of bisphosphonates. *Breast Cancer Res* 2002; 4: 30–34.
2. Civitelli R, Napoli N, Armamento-Villareal R. Use of intravenous bisphosphonates in osteoporosis. *Curr Osteoporos Rep* 2007; 5: 8–13.

3. Green JR. Bisphosphonates: preclinical review. *Oncologist* 2004; 9 (Suppl 4): 3–13.
4. Rogers MJ, Brown RJ, Hodkin V et al. Bisphosphonates are incorporated into adenine nucleotides by human aminoacyl-tRNA synthetase enzymes. *Biochem Biophys Res Commun* 1996; 224: 863–869.
5. Luckman SP, Hughes DE, Coxon FP et al. Nitrogen-containing bisphosphonates inhibit the mevalonate pathway and prevent post-translational prenylation of GTP-binding proteins, including Ras. *J Bone Miner Res* 1998; 13: 581–589.
6. Goffinet M, Thoulouzan M, Pradines A et al. Zoledronic acid treatment impairs protein geranyl-geranylation for biological effects in prostatic cells. *BMC Cancer* 2006; 6: 60.
7. Coleman RE. Bisphosphonates: clinical experience. *Oncologist* 2004; 9 (Suppl 4): 14–27.
8. Coleman RE. Skeletal complications of malignancy. *Cancer* 1997; 80: 1588–1594.
9. Body JJ. Current and future directions in medical therapy: hypercalcemia. *Cancer* 2000; 88: 3054–3058.
10. Body JJ. Hypercalcemia of malignancy. *Semin Nephrol* 2004; 24: 48–54.
11. Saad F, Olsson C, Schulman CC. Skeletal morbidity in men with prostate cancer: quality-of-life considerations throughout the continuum of care. *Eur Urol* 2004; 46: 731–739 discussion 739–740.
12. Weinfurt KP, Castel LD, Li Y et al. Health-related quality of life among patients with breast cancer receiving zoledronic acid or pamidronate disodium for metastatic bone lesions. *Med Care* 2004; 42: 164–175.
13. Wardley A, Davidson N, Barrett-Lee P et al. Zoledronic acid significantly improves pain scores and quality of life in breast cancer patients with bone metastases: a randomised, crossover study of community vs hospital bisphosphonate administration. *Br J Cancer* 2005; 92: 1869–1876.
14. Delea T, Langer C, McKiernan J et al. The cost of treatment of skeletal-related events in patients with bone metastases from lung cancer. *Oncology* 2004; 67: 390–396.
15. Gralow J, Tripathy D. Managing metastatic bone pain: the role of bisphosphonates. *J Pain Symptom Manage* 2007; 33: 462–472.
16. Botteman M, Barghout V, Stephens J et al. Cost effectiveness of bisphosphonates in the management of breast cancer patients with bone metastases. *Ann Oncol* 2006; 17: 1072–1082.
17. De Cock E, Hutton J, Canney P et al. Cost-effectiveness of oral ibandronate versus IV zoledronic acid or IV pamidronate for bone metastases in patients receiving oral hormonal therapy for breast cancer in the United Kingdom. *Clin Ther* 2005; 27: 1295–1310.
18. Souberbielle B, Williams R, McCloskey E. The cost-effectiveness of bisphosphonates in metastatic breast cancer: letter to the editor in response to Botteman et al. 2006. *Ann Oncol* 2007; 18: 393.
19. Gnant MF, Milneritsch B, Luschin-Ebengreuth G et al. Zoledronic acid prevents cancer treatment-induced bone loss in premenopausal women receiving adjuvant endocrine therapy for hormone-responsive breast cancer: a report from the Austrian Breast and Colorectal Cancer Study Group. *J Clin Oncol* 2007; 25: 820–828.
20. Brufsky A. Management of cancer-treatment-induced bone loss in postmenopausal women undergoing adjuvant breast cancer therapy: a Z-FAST update. *Semin Oncol* 2006; 33: S13–S17.
21. Brufsky A, Harker WG, Beck JT et al. Zoledronic acid inhibits adjuvant letrozole-induced bone loss in postmenopausal women with early breast cancer. *J Clin Oncol* 2007; 25: 829–836.
22. Powles T, McCroskey E, Paterson A. Oral bisphosphonates as adjuvant therapy for operable breast cancer. *Clin Cancer Res* 2006; 12: 6301s–6304s.
23. Diel IJ. Bisphosphonates in the prevention of bone metastases: current evidence. *Semin Oncol* 2001; 28: 75–80.
24. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. *Cancer Treat Rev* 2001; 27: 165–176.
25. Hei YJ, Saad F, Coleman RE, Chen YM. Fractures negatively affect survival in patients with bone metastases from breast cancer. *Breast Cancer Res Treat* 2005; 94: (Abstr 6036).
26. Kohno N, Aogi K, Minami H et al. Zoledronic acid significantly reduces skeletal complications compared with placebo in Japanese women with bone metastases from breast cancer: a randomized, placebo-controlled trial. *J Clin Oncol* 2005; 23: 3314–3321.
27. Wong R, Wiffen PJ. Bisphosphonates for the relief of pain secondary to bone metastases (Cochrane Review). *The Cochrane Library*. Chichester, UK: John Wiley & Sons 2004; 1–59.
28. Body JJ, Diel IJ, Bell R et al. Oral ibandronate improves bone pain and preserves quality of life in patients with skeletal metastases due to breast cancer. *Pain* 2004; 111: 306–312.
29. Hortobagyi GN, Theriault RL, Lipton A et al. Long-term prevention of skeletal complications of metastatic breast cancer with pamidronate. Protocol 19 Aredia Breast Cancer Study Group. *J Clin Oncol* 1998; 16: 2038–2044.
30. Body JJ, Diel IJ, Lichinitser MR et al. Intravenous ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases. *Ann Oncol* 2003; 14: 1399–1405.
31. Body JJ, Diel IJ, Lichinitser M 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: 1133–1137.
32. Kristensen B, Ejlersen B, Groenvold M et al. Oral clodronate in breast cancer patients with bone metastases: a randomized study. *J Intern Med* 1999; 246: 67–74.
33. Paterson AH, Powles TJ, Kanis JA et al. Double-blind controlled trial of oral clodronate in patients with bone metastases from breast cancer. *J Clin Oncol* 1993; 11: 59–65.
34. Tubiana-Hulin M, Beuzeboc P, Mauriac L et al. Double-blinded controlled study comparing clodronate versus placebo in patients with breast cancer bone metastases. *Bull Cancer* 2001; 88: 701–707.
35. Theriault RL, Lipton A, Hortobagyi GN 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: 846–854.
36. Rosen LS, Gordon D, Kaminski M 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: 1735–1744.
37. Pavlakis N, Schmidt R, Stockler M. Bisphosphonates for breast cancer. *Cochrane Database Syst Rev* 2005; CD003474.
38. Body J-J. Breast cancer: bisphosphonate therapy for metastatic bone disease. *Clin Cancer Res* 2006; 12: 6258s–6263s.
39. Lipton A, Theriault RL, Hortobagyi GN 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: 1082–1090.
40. Rosen LS, Gordon D, Kaminski M 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: 377–387.
41. Rosen LS, Gordon DH, Dugan W Jr 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.
42. Body JJ, Lichinitser M, Tjulandin S et al. 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 (7): 1165–1170.
43. Paterson AH, Ernst DS, Powles TJ et al. Treatment of skeletal disease in breast cancer with clodronate. *Bone* 1991; 12 (Suppl 1): S25–S30.
44. Yuen KK, Shelley M, Sze WM et al. Bisphosphonates for advanced prostate cancer. *Cochrane Database Syst Rev* 2006; CD006250.
45. Elomaa I, Kylmala T, Tammela T et al. Effect of oral clodronate on bone pain. A controlled study in patients with metastatic prostatic cancer. *Int Urol Nephrol* 1992; 24: 159–166.
46. Dearnaley DP, Sydes MR, Mason MD et al. A double-blind, placebo-controlled, randomized trial of oral sodium clodronate for metastatic prostate cancer (MRC PR05 Trial). *J Natl Cancer Inst* 2003; 95: 1300–1311.

47. Ernst DS, Brasher P, Hagen N et al. A randomized, controlled trial of intravenous clodronate in patients with metastatic bone disease and pain. *J Pain Symptom Manage* 1997; 13: 319–326.
48. Smith JA Jr. Palliation of painful bone metastases from prostate cancer using sodium etidronate: results of a randomized, prospective, double-blind, placebo-controlled study. *J Urol* 1989; 141: 85–87.
49. Heidenreich A, Eler T, Hofmann R. Ibandronate in the treatment of prostate cancer associated painful osseous metastases. *Prostate Cancer Prostatic Dis* 2002; 5: 231–235.
50. Heidenreich A, Ohlmann C, Body JJ. Ibandronate in metastatic bone pain. *Semin Oncol* 2004; 31: 67–72.
51. Small EJ, Smith MR, Seaman JJ et al. Combined analysis of two multicenter, randomized, placebo-controlled studies of pamidronate disodium for the palliation of bone pain in men with metastatic prostate cancer. *J Clin Oncol* 2003; 21: 4277–4284.
52. Saad F, Gleason DM, Murray R 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: 879–882.
53. Saad F. Clinical benefit of zoledronic acid for the prevention of skeletal complications in advanced prostate cancer. *Clin Prostate Cancer* 2005; 4: 31–37.
54. Saad F, Gleason DM, Murray R et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst* 2002; 94: 1458–1468.
55. Ernst DS, Tannock IF, Winquist EW et al. Randomized, double-blind, controlled trial of mitoxantrone/prednisone and clodronate versus mitoxantrone/prednisone and placebo in patients with hormone-refractory prostate cancer and pain. *J Clin Oncol* 2003; 21: 3335–3342.
56. Saad F, Gleason D, Murray R, Tchekmedyian S. Zoledronic acid reduces skeletal morbidity regardless of previous skeletal events in men with prostate cancer and bone metastases [poster]. Paris, France: Presented at: 21st Annual Congress of the European Association of Urology 2006 April 5–8 (Abstr 141).
57. Saad F. Bisphosphonates can prevent skeletal complications of malignant bone disease from prostate cancer and renal cell carcinoma. *Eur Urol Suppl* 2007; 6: 683–688.
58. Rosen LS, Gordon D, Tchekmedyian S 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: 3150–3157.
59. Rosen LS, Gordon D, Tchekmedyian NS 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: 2613–2621.
60. Zekri J, Ahmed N, Coleman RE, Hancock BW. The skeletal metastatic complications of renal cell carcinoma. *Int J Oncol* 2001; 19: 379–382.
61. Bell R. Efficacy of ibandronate in metastatic bone disease: review of clinical data. *Oncologist* 2005; 10 (Suppl 1): 8–13.
62. Piga A, Bracci R, Ferretti B et al. A double blind randomized study of oral clodronate in the treatment of bone metastases from tumors poorly responsive to chemotherapy. *J Exp Clin Cancer Res* 1998; 17: 213–217.
63. Summary of product characteristics (SmPC) Clodronate, Bonafos®. Swissmedic (50957, 50958). 2006. <http://www.kompndium.ch/Search.aspx?lang=de>.
64. Summary of product characteristics (SmPC) Ibandronate, Bondronat®. Swissmedic (53626, 53630, 57424). 2007. <http://www.kompndium.ch/Search.aspx?lang=de>.
65. Emkey RD, Ettinger M. Improving compliance and persistence with bisphosphonate therapy for osteoporosis. *Am J Med* 2006; 119: S18–S–24.
66. Cramer JA, Gold DT, Silverman SL et al. A systematic review of persistence and compliance with bisphosphonates for osteoporosis. *Osteoporos Int* 2007; 18 (8): 1023–1031.
67. Gold DT, Safi W, Trinh H. Patient preference and adherence: comparative US studies between two bisphosphonates, weekly risedronate and monthly ibandronate. *Curr Med Res Opin* 2006; 22: 2383–2391.
68. Cooper A, Drake J, Brankin E. Treatment persistence with once-monthly ibandronate and patient support vs. once-weekly alendronate: results from the PERSIST study. *Int J Clin Pract* 2006; 60: 896–905.
69. Göl D. Poor persistency with oral bisphosphonates in cancer patients with bone metastasis. *Proc Am Soc Clin Oncol* 2004 (Abstr 8221).
70. Mangiapane S, Hoer A, Gothe H et al. Higher persistency with i.v. bisphosphonates in patients with bone metastasis. *ASCO Meeting Abstracts* 2006; 24: 18623.
71. Chern B, Joseph D, Joshua D et al. Bisphosphonate infusions: patient preference, safety and clinic use. *Support Care Cancer* 2004; 12: 463–466.
72. Summary of product characteristics (SmPC) Zoledronic Acid, Zometa®. Swissmedic (56257). 2005. <http://www.kompndium.ch/Search.aspx?lang=de>.
73. Summary of product characteristics (SmPC) Pamidronate, Aredia®. Swissmedic (52092). 2005. <http://www.kompndium.ch/Search.aspx?lang=de>.
74. Bondronat (ibandronic acid), Summary of Product Characteristics, 5 (IA) (EU/1/96/012/004 and EU/1/96/009-013). Welwyn Garden City, UK: Roche Registration, Ltd. Updated on March 6, 2007 based on EMEA/H/C/101/IA/043.
75. Body JJ, Mancini I. Bisphosphonates for cancer patients: why, how, and when? *Support Care Cancer* 2002; 10: 399–407.
76. Hirsh V, Tchekmedyian NS, Rosen LS et al. Clinical benefit of zoledronic acid in patients with lung cancer and other solid tumors: analysis based on history of skeletal complications. *Clin Lung Cancer* 2004; 6: 170–174.
77. Clemons MJ, Dranitsaris G, Ooi WS et al. Phase II trial evaluating the palliative benefit of second-line zoledronic acid in breast cancer patients with either a skeletal-related event or progressive bone metastases despite first-line bisphosphonate therapy. *J Clin Oncol* 2006; 24: 4895–4900.
78. Clemons M, Dranitsaris G, Ooi W, Cole DE. A phase II trial evaluating the palliative benefit of second-line oral ibandronate in breast cancer patients with either a skeletal related event (SRE) or progressive bone metastases (BM) despite standard bisphosphonate (BP) therapy. *Breast Cancer Res Treat* 2007.
79. Coleman RE, Major P, Lipton A et al. Predictive value of bone resorption and formation markers in cancer patients with bone metastases receiving the bisphosphonate zoledronic acid. *J Clin Oncol* 2005; 23: 4925–4935.
80. Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. *Clin Cancer Res* 2006; 12: 6243s–6249s.
81. Cook RJ, Coleman R, Brown J et al. Markers of bone metabolism and survival in men with hormone-refractory metastatic prostate cancer. *Clin Cancer Res* 2006; 12: 3361–3367.
82. Body JJ, Coleman R, Clezardin P et al. International Society of Geriatric Oncology (SIOG) clinical practice recommendations for the use of bisphosphonates in elderly patients. *Eur J Cancer* 2007; 43: 852–858.
83. Weinfurt KP, Li Y, Castel LD et al. The significance of skeletal-related events for the health-related quality of life of patients with metastatic prostate cancer. *Ann Oncol* 2005; 16: 579–584.
84. Chow SC, Ki FY. Statistical issues in quality-of-life assessment. *J Biopharm Stat* 1996; 6: 37–48.
85. Chow E, Hoskin P, van der Linden Y et al. Quality of life and symptom end points in palliative bone metastases trials. *Clin Oncol (R Coll Radiol)* 2006; 18: 67–69.
86. Chow E, Harris K, Tharmalingam S et al. Early phase in the development of a bone metastases quality of life module. *Clin Oncol (R Coll Radiol)* 2007; 19: S26.
87. WHO's pain relief ladder. <http://www.who.int/cancer/palliative/painladder/en/>.
88. Body JJ. Bisphosphonates for metastatic bone pain. *Support Care Cancer* 1999; 7: 1–3.
89. Vassiliou V, Kalogeropoulou C, Christopoulos C et al. Combination ibandronate and radiotherapy for the treatment of bone metastases: clinical evaluation and radiologic assessment. *Int J Radiat Oncol Biol Phys* 2007; 67: 264–272.
90. Vassiliou V, Kalogeropoulou C, Giannopoulou E et al. A novel study investigating the therapeutic outcome of patients with lytic, mixed and sclerotic bone metastases treated with combined radiotherapy and ibandronate. *Clin Exp Metastasis* 2007; 24 (3): 169–178.

91. Heidenreich A, Hofmann R, Engelmann UH. The use of bisphosphonate for the palliative treatment of painful bone metastasis due to hormone refractory prostate cancer. *J Urol* 2001; 165: 136–140.
92. Mancini I, Dumon JC, Body JJ. Efficacy and safety of ibandronate in the treatment of opioid-resistant bone pain associated with metastatic bone disease: a pilot study. *J Clin Oncol* 2004; 22: 3587–3592.
93. Daubine F, Le Gall C, Gasser J et al. Antitumor effects of clinical dosing regimens of bisphosphonates in experimental breast cancer bone metastasis. *J Natl Cancer Inst* 2007; 99: 322–330.
94. Bauss F, Body JJ. Ibandronate in metastatic bone disease: a review of preclinical data. *Anticancer Drugs* 2005; 16: 107–118.
95. Jagdev SP, Coleman RE, Shipman CM et al. The bisphosphonate, zoledronic acid, induces apoptosis of breast cancer cells: evidence for synergy with paclitaxel. *Br J Cancer* 2001; 84: 1126–1134.
96. Ullén A, Lennartsson L, Hjelm-Eriksson M et al. Additive/synergistic anti-tumoral effects on prostate cancer cells in vitro following treatment with a combination of gemcitabine and zoledronic acid. *Proc Am Soc Clin Oncol* 2003; 22: 432 (Abstr 1737).
97. Neville-Webbe HL, Evans CA, Coleman RE, Holen I. Mechanisms of the synergistic interaction between the bisphosphonate zoledronic acid and the chemotherapy agent paclitaxel in breast cancer cells in vitro. *Tumour Biol* 2006; 27: 92–103.
98. Neville-Webbe HL, Rostami-Hodjegan A, Evans CA et al. Sequence- and schedule-dependent enhancement of zoledronic acid induced apoptosis by doxorubicin in breast and prostate cancer cells. *Int J Cancer* 2005; 113: 364–371.
99. Vogt U, Bielawski KP, Bosse U, Schlotter CM. Breast tumour growth inhibition in vitro through the combination of cyclophosphamide/metotrexate/5-fluorouracil, epirubicin/cyclophosphamide, epirubicin/paclitaxel, and epirubicin/docetaxel with the bisphosphonates ibandronate and zoledronic acid. *Oncol Rep* 2004; 12: 1109–1114.
100. Journe F, Magne N, Chaboteaux C et al. Sequence- and concentration-dependent effects of acute and long-term exposure to the bisphosphonate ibandronate in combination with single and multiple fractions of ionising radiation doses in human breast cancer cell lines. *Clin Exp Metastasis* 2006; 23: 135–147.
101. Iuliano F, Molica S, Abruzzese E et al. Samarium-153Sm-EDTMP and zoledronic acid present synergistic action and are able to control pain and significantly improve QoL in elderly patients with MM. (Results of a phase II trial and 19 months follow up). *J Clin Oncol (Meeting Abstracts)* 2004; 22: 6737.
102. Dunstan C, Felsenberg D, Seibel MJ. Therapy insight: the risks and benefits of bisphosphonates for the treatment of tumor-induced bone disease. *Nat Clin Pract Oncol* 2006; 4: 42–55.
103. Hewitt RE, Lissina A, Green AE et al. The bisphosphonate acute phase response: rapid and copious production of proinflammatory cytokines by peripheral blood gd T cells in response to aminobisphosphonates is inhibited by statins. *Clin Exp Immunol* 2005; 139: 101–111.
104. Adami S, Bhalla AK, Dorizzi R et al. The acute-phase response after bisphosphonate administration. *Calcif Tissue Int* 1987; 41: 326–331.
105. Chang JT, Green L, Beitz J. Renal failure with the use of zoledronic acid. *N Engl J Med* 2003; 349: 1676–1679; discussion 1676–1679.
106. Zojer N, Keck AV, Pecherstorfer M. Comparative tolerability of drug therapies for hypercalcaemia of malignancy. *Drug Saf* 1999; 21: 389–406.
107. Vogel CL, Yanagihara RH, Wood AJ et al. Safety and pain palliation of zoledronic acid in patients with breast cancer, prostate cancer, or multiple myeloma who previously received bisphosphonate therapy. *Oncologist* 2004; 9: 687–695.
108. Pecherstorfer M, Diel IJ. Rapid administration of ibandronate does not affect renal functioning: evidence from clinical studies in metastatic bone disease and hypercalcaemia of malignancy. *Support Care Cancer* 2004; 12: 877–881.
109. Pecherstorfer M, Rivkin S, Body JJ et al. Long-term safety of intravenous ibandronic acid for up to 4 years in metastatic breast cancer: an open-label trial. *Clin Drug Invest* 2006; 26: 315–322.
110. von Moos R, Thürlimann B, Caspar CB et al. Renal safety of intravenous ibandronate 6mg infused over 15 or 60 minutes in patients with breast cancer and bone metastases: a randomized, open-label study. *ASCO Annual Meeting Proceedings Part I. J Clin Oncol* 2007; 25 (18 Suppl): (Abstr 1114).
111. Woo SB, Hellstein JW, Kalmar JR. Narrative [corrected] review: bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med* 2006; 144: 753–761.
112. Van den Wyngaert T, Huizing MT, Vermorcken JB. Bisphosphonates and osteonecrosis of the jaw: cause and effect or a post hoc fallacy? *Ann Oncol* 2006; 17: 1197–1204.
113. Ruggiero SL, Fantasia J, Carlson E. Bisphosphonate-related osteonecrosis of the jaw: background and guidelines for diagnosis, staging and management. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006; 102: 433–441.
114. Lenz JH, Steiner-Krammer B, Schmidt W et al. Does avascular necrosis of the jaws in cancer patients only occur following treatment with bisphosphonates? *J Craniomaxillofac Surg* 2005; 33: 395–403.
115. Koka S, Clarke BL, Amin S et al. Oral bisphosphonate therapy and osteonecrosis of the jaw: what to tell the concerned patient. *Int J Prosthodont* 2007; 20: 115–122.
116. Weitzman R, Sauter N, Eriksen EF. Critical review: updated recommendations for the prevention, diagnosis, and treatment of osteonecrosis of the jaw in cancer patients—May 2006. *Crit Rev Oncol Hematol* 2007; 62: 148–152.
117. Montazeri AH, Erskine JG, McQuaker IG. Oral sodium clodronate induced osteonecrosis of the jaw in a patient with myeloma. *Eur J Haematol* 2007; 79: 69–71.
118. Hansen T, Kunkel M, Weber A, James Kirkpatrick C. Osteonecrosis of the jaws in patients treated with bisphosphonates—histomorphologic analysis in comparison with infected osteoradionecrosis. *J Oral Pathol Med* 2006; 35: 155–160.
119. Bilezikian JP. Osteonecrosis of the jaw—do bisphosphonates pose a risk? *N Engl J Med* 2006; 355: 2278–2281.
120. Zheng Y, Zhou H, Brennan K et al. Inhibition of bone resorption, rather than direct cytotoxicity, mediates the anti-tumour actions of ibandronate and osteoprotegerin in a murine model of breast cancer bone metastasis. *Bone* 2007; 40: 471–478.
121. Friedlaender GE, Tross RB, Doganis AC et al. Effects of chemotherapeutic agents on bone. I. Short-term methotrexate and doxorubicin (adriamycin) treatment in a rat model. *J Bone Joint Surg Am* 1984; 66: 602–607.
122. Delmas PD, Fontana A. Bone loss induced by cancer treatment and its management. *Eur J Cancer* 1998; 34: 260–262.
123. Pfeilschifter J, Diel IJ. Osteoporosis due to cancer treatment: pathogenesis and management. *J Clin Oncol* 2000; 18: 1570–1593.
124. Thürlimann B, Keshaviah A, Coates AS et al. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. *N Engl J Med* 2005; 353: 2747–2757.
125. Howell A, Cuzick J, Baum M et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 2005; 365: 60–62.
126. Coleman RE, Banks LM, Girgis SI et al. Skeletal effects of exemestane on bone-mineral density, bone biomarkers, and fracture incidence in postmenopausal women with early breast cancer participating in the Intergroup Exemestane Study (IES): a randomised controlled study. *Lancet Oncol* 2007; 8: 119–127.
127. Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med* 2005; 352: 154–164.
128. Eastell R, Hannon RA, Cuzick J et al. Effect of an aromatase inhibitor on bmd and bone turnover markers: 2-year results of the Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial (18233230). *J Bone Miner Res* 2006; 21: 1215–1223.
129. Kanis JA, McCloskey EV. Clodronate. *Cancer* 1997; 80: 1691–1695.
130. Smith MR, McGovern FJ, Zietman AL et al. Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. *N Engl J Med* 2001; 345: 948–955.
131. Cummings SR, Browner WS, Bauer D et al. Endogenous hormones and the risk of hip and vertebral fractures among older women. Study of Osteoporotic Fractures Research Group. *N Engl J Med* 1998; 339: 733–738.
132. Hoff AO, Gagel RF. Osteoporosis in breast and prostate cancer survivors. *Oncology (Williston Park)* 2005; 19: 651–658.

133. Saarto T, Blomqvist C, Valimaki M et al. Clodronate improves bone mineral density in post-menopausal breast cancer patients treated with adjuvant antiestrogens. *Br J Cancer* 1997; 75: 602–605.
134. Delmas PD, Balena R, Confavreux E et al. Bisphosphonate risedronate prevents bone loss in women with artificial menopause due to chemotherapy of breast cancer: a double-blind, placebo-controlled study. *J Clin Oncol* 1997; 15: 955–962.
135. Powles TJ, McCloskey E, Paterson AH et al. Oral clodronate and reduction in loss of bone mineral density in women with operable primary breast cancer. *J Natl Cancer Inst* 1998; 90: 704–708.
136. Greenspan SL, Nelson JB, Trump DL, Resnick NM. Effect of once-weekly oral alendronate on bone loss in men receiving androgen deprivation therapy for prostate cancer: a randomized trial. *Ann Intern Med* 2007; 146: 416–424.
137. Gnant MF, Mlineritsch B, Luschin-Ebengreuth G et al. Zoledronic acid effectively prevents cancer treatment-induced bone loss in premenopausal women receiving adjuvant endocrine therapy for hormone-responsive breast cancer: a report from the Austrian Breast and Colorectal Cancer Study Group. *J Clin Oncol* 2007; 25 (7): 820–828.
138. Brufsky A, Harker WG, Beck JT et al. Zoledronic acid inhibits adjuvant letrozole-induced bone loss in postmenopausal women with early breast cancer. *J Clin Oncol* 2007; 25 (7): 829–836.
139. Brufsky A, Bundred N, Coleman R. An integrated analysis of zoledronic acid for prevention of aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole. *Breast Cancer Res Treat* 2006; 100 (Suppl 1): S25.
140. Michaelson MD, Kaufman DS, Lee H et al. Randomized controlled trial of annual zoledronic acid to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer. *J Clin Oncol* 2007; 25: 1038–1042.
141. Smith MR, Eastham J, Gleason DM et al. Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. *J Urol* 2003; 169: 2008–2012.
142. McCloskey E, Paterson AHG, Powles TJ. Oral clodronate maintains bone mass in women with primary breast cancer. *J Clin Oncol* 2005; 23 (Abstr 535).
143. McCloskey E, Paterson AHG, Powles TJ. Effects of oral clodronate (BONEFOS (R)) therapy on bone turnover and skeletal metastases in women with primary breast cancer. *Breast Cancer Res Treat* 2005; 94 (Suppl 1): 5 (Abstr 43).
144. Lester JE, Gatcher SA, Ellis SP et al. Effect of monthly oral ibandronate on anastrozole-induced bone loss during adjuvant treatment for breast cancer: One-year results from the ARIBON study. *J Clin Oncol* (Meeting Abstracts) 2007; 25: (Abstr 553).
145. Aapro M, Hadji P, Brufsky A et al. Recommendation for the prevention of Aromatase Inhibitor associated Bone Loss in women with Breast Cancer. Submitted Poster Presentation, ECCO 14, 2007.
146. Diel IJ, Solomayer EF, Costa SD et al. Reduction in new metastases in breast cancer with adjuvant clodronate treatment. *N Engl J Med* 1998; 339: 357–363.
147. Saarto T, Vehmanen L, Virkkunen P, Blomqvist C. Ten-year follow-up of a randomized controlled trial of adjuvant clodronate treatment in node-positive breast cancer patients. *Acta Oncol* 2004; 43: 650–656.
148. Powles T, Paterson A, McCloskey E et al. Reduction in bone relapse and improved survival with oral clodronate for adjuvant treatment of operable breast cancer [SRCTN83688026]. *Breast Cancer Res* 2006; 8: R13.
149. Saarto T, Vehmanen L, Blomqvist C, Elomaa I. 10-year follow-up of the efficacy of clodronate on bone mineral density (BMD) in early stage breast cancer. *J Clin Oncol ASCO Annual Meeting Proceedings Part I* 2006; 24 (18 Suppl): (Abstr 676).
150. Jaschke A, Bastert G, Solomayer EF et al. Adjuvant clodronate treatment improves the overall survival of primary breast cancer patients with micrometastases to bone marrow—a longtime follow-up. *J Clin Oncol* (Meeting Abstracts) 2004; 22: 529.
151. Ha TC, Li H. Meta-analysis of clodronate and breast cancer survival. *Br J Cancer* 2007; 96: 1796–1801.
152. Mystakidou K, Katsouda E, Parpa E et al. Randomized, open label, prospective study on the effect of zoledronic acid on the prevention of bone metastases in patients with recurrent solid tumors that did not present with bone metastases at baseline. *Med Oncol* 2005; 22: 195–201.
153. Rack W, Janni A, Schoberth C et al. Effect of zoledronate on persisting isolated tumor cells (ITC) in the bone marrow (BM) of patients without recurrence of early breast cancer. *Proc Am Soc Clin Oncol* 2004; 23 (Suppl): 843 (Abstract 9515).
154. Coleman R, Thorpe H, Cameron D et al. Zoledronic acid is well tolerated and can be safely administered with adjuvant chemotherapy—first safety data from the AZURE trial (BIG01/04) [poster] Presented at: 29th Annual San Antonio Breast Cancer Symposium; San Antonio, TX; December 14–17, 2006 (Abstr 2080).