

Denosumab for the treatment of bone metastases in breast cancer: evidence and opinion

Guenther G. Steger and Rupert Bartsch

Abstract:

Introduction: Denosumab, a fully human monoclonal antibody, targets the receptor activator of nuclear factor-kappaB (RANK) ligand, a protein essential for osteoclast differentiation, activity and survival. Loss of osteoclasts from the bone surface reduces bone turnover and bone loss in malignant and benign diseases. In breast cancer, bone metastases are frequently observed; cancer treatment-induced bone loss (CTIBL) may result as a consequence of endocrine treatment or chemotherapy. Furthermore, preclinical studies suggest a direct role of the RANK/RANK-ligand pathway in breast tumorigenesis. This paper reviews preclinical and clinical data on denosumab in breast cancer.

Materials and methods: Studies were identified through the Medline database. Key search terms included: AMG-162, bisphosphonates, denosumab, RANK-ligand and zoledronic acid. Information available in abstract form only was retrieved from major oncology meetings, such as the American Society of Clinical Oncology (ASCO) annual meeting, ASCO breast meeting, European Cancer Organization, European Society of Medical Oncology and the San Antonio Breast Cancer Symposium.

Results: Denosumab was consistently well tolerated throughout clinical trials, although the observed incidence of osteonecrosis of the jaw was comparable to that with bisphosphonates. Efficacy as determined by a reduction of skeletal-related events was at least equal to zoledronic acid, and superior in one phase III study conducted in patients with metastatic breast cancer. Clinical trials investigating the role of denosumab for the prevention of CTIBL and breast cancer recurrences are currently ongoing.

Conclusion: In conclusion, denosumab appears to be an effective and safe treatment option in patients with bone metastases from breast cancer with the potential of also preventing CTIBL.

Keywords: bisphosphonates, bone metastases, cancer treatment-induced bone loss, denosumab, osteoporosis, receptor activator of nuclear factor-kappaB

Introduction

Breast cancer

Breast cancer is the most common malignant disease in women worldwide [American Cancer Society, 2009]. Bone loss and bone degradation are frequently observed in breast cancer patients and occur as a treatment side effect, that is, cancer treatment induced bone loss (CTIBL) [Amir *et al.* 2010] or directly due to bone metastases [Coleman, 2001]. Bone resorption requires osteoclasts, cells specialized in the degradation of bone tissue. Osteoclast activation is triggered by

the receptor activator of nuclear factor-kappaB (RANK)/RANK-ligand pathway, rendering RANK-ligand an attractive target for the prevention of bone loss. Recent preclinical data suggest that this pathway may also play a role in breast tumorigenesis, opening the stage for new options of breast cancer prophylaxis and therapy [Beleut *et al.* 2010; Schramek *et al.* 2010].

Bone metastases in breast cancer

Bone metastases are common in breast cancer; indeed, up to 60% of patients with advanced breast cancer will eventually develop bone

Ther Adv Med Oncol

(2011) 3(5) 233–243

DOI: 10.1177/

1758834011412656

© The Author(s), 2011.
Reprints and permissions:
[http://www.sagepub.co.uk/
journalsPermissions.nav](http://www.sagepub.co.uk/journalsPermissions.nav)

Correspondence to:
Guenther G. Steger, MD
Department of Medicine,
Clinical Division of
Oncology, Comprehensive
Cancer Centre, Medical
University of Vienna,
Waehringer Guertel
18–20, A-1090 Vienna,
Austria
[guenther.steger@
meduniwien.ac.at](mailto:guenther.steger@meduniwien.ac.at)

Rupert Bartsch, MD
Department of Medicine,
Clinical Division of
Oncology, Comprehensive
Cancer Centre, Medical
University of Vienna,
Vienna, Austria

metastases during their course of disease [Coleman, 2001]. According to radiographic appearance, lesions are classified as being osteolytic, osteoblastic or mixed [Roodman, 2004], with the majority of breast cancer bone metastases belonging to the mixed or lytic types [Yin *et al.* 2005]. Therefore, complications such as hypercalcaemia, fractures or spinal cord compressions may occur [Mundy, 2001]. Fractures as well as spinal cord compression and the consecutive local interventions (e.g. surgery to bone, radiotherapy to bone) are summarized by the term 'skeletal-related events' (SREs) [Ross *et al.* 2003]. In most phase III clinical trials, reduction of SREs is chosen as the primary endpoint in order to measure the activity of drugs blocking bone resorption. In phase I and II studies, biomarkers of bone turnover, for example, urinary-N-telopeptide/creatinine ratio (uNTX/Cr), are often substituted as a surrogate endpoint [Brown *et al.* 2003].

Current treatment options for bone metastases

Apart from systemic antitumour therapy and local interventions, bisphosphonates and denosumab were developed as direct inhibitors of bone resorption. Through different mechanisms of action, these bone-specific agents block osteoclast function. Bisphosphonates have a unique property of selective uptake by their target organ. After binding strongly to hydroxyapatite bone mineral, they are internalized by osteoclasts located on the bone surface [Baron *et al.* 2011]. Once taken up, bisphosphonates that contain a nitrogen residue on a side chain (amino-bisphosphonates) inhibit the enzyme farnesyl-pyrophosphate synthase within osteoclasts, thereby preventing prenylation of certain signal-transduction GTPases, such as Ras, Rho and Rac, which, in turn, induces apoptosis [Luckmann *et al.* 1998]. Non-nitrogen-containing bisphosphonates, on the other hand, are metabolized into ATP analogues, which again eventually leads to cell degradation [Frith *et al.* 2001].

In contrast, denosumab acts by blocking osteoclast differentiation from osteoclast precursor cells [Bekker *et al.* 2004]. This mechanism and its clinical relevance will be discussed in this article.

CTIBL

Under physiological conditions, a postmenopausal woman loses 1% of bone mass per year

[Kanis *et al.* 1997]. Tamoxifen was regarded as the standard of care for the treatment of endocrine-responsive breast cancer for nearly two decades. This selective oestrogen receptor modulator exhibits antiresorptive properties in bone tissue, thereby preventing the development of osteoporosis. Aromatase inhibitors, however, are superior to tamoxifen as adjuvant therapy for early breast cancer [Thürlimann *et al.* 2005]. This class of drugs acts by blocking aromatase, the main source of oestrogen production in postmenopausal women. Reduction of oestrogen blood levels, on the other hand, increases annual bone loss to 2.6% [Eastell *et al.* 2006; Perez *et al.* 2006]. This is clinically relevant, as such bone loss eventually translates into higher fracture rates (11% in patients treated with aromatase inhibitors compared with 8% on tamoxifen) [Howell *et al.* 2005].

CTIBL may also occur in premenopausal women due to chemotherapy-induced ovarian failure [Hines *et al.* 2009] or suppression of ovarian function by gonadotropin-releasing hormone analogues [Gnant *et al.* 2007]. Furthermore, fracture rates are increased by androgen deprivation in male patients with prostate cancer [Smith *et al.* 2009].

Bisphosphonates, when given in conjunction with endocrine therapy, prevent CTIBL as evidenced by a decreased reduction of bone mineral density [Van Poznak *et al.* 2010; Gnant *et al.* 2007]. Other trials even observed an increase of bone mineral density in patients receiving bisphosphonates [Eidtmann *et al.* 2010; Brufsky *et al.* 2009]. However, this effect might not translate into a reduction in fracture rates [Valachis *et al.* 2010]. In this context, however, it is important to realize that the reason such a decrease in fracture rates was not observed may be related to the fact that bisphosphonates in most trials were only initiated when patients developed a *T*-score of less than -2.0. Furthermore, many of those studies were not adequately powered to detect such an effect. Denosumab on the other hand was found to reduce the incidence of new vertebral fractures in prostate cancer patients on androgen deprivation in a large, adequately powered phase III study [Smith *et al.* 2009]. Phase III clinical trials of denosumab for the prevention of CTIBL in breast cancer are currently ongoing [ClinicalTrials.gov identifier: NCT0056374; Bartsch and Steger 2009].

Bone metabolism

Osteoclast activation

As outlined, osteoclasts are key mediators of bone resorption. Osteoclasts derive from osteoclast precursors (OCPs). Those cells derive from bone marrow cells of mononuclear lineage, linking bone metabolism with the immune system. Under physiological conditions, a balance of bone synthesis and degradation exists; therefore, osteoblasts were suggested to mediate osteoclast activation via a hypothetical ‘osteoclast activating factor’ [Rodan and Martin, 1981]. This assumption was eventually proven correct when the RANK-ligand was identified (reviewed by Geusens [2009]). This protein is part of a system of interacting cytokines of the tumour necrosis factor (TNF) family that regulates bone turnover. In the RANK/RANK-ligand pathway, RANK-ligand, which is secreted by osteoblasts and bone marrow stromal cells, activates RANK on the surface of OCPs, inducing differentiation of precursors into mature cells. This step is antagonized by osteoprotegerin (OPG) (reviewed by Vega *et al.* [2007]).

RANK/RANKL/OPG pathway in breast cancer bone metastases

In breast cancer bone metastases, the interaction of tumour cells, bone matrix and bone cells results in a vicious cycle of bone destruction [Giuliano *et al.* 2004]. Tumour cells secrete cytokines and growth factors, such as parathyroid hormone-related peptide, interleukin (IL)-1, IL-6, IL-8, IL11 and TNF- α , thereby causing stroma cells and osteoblasts to secrete RANK-ligand

[Kitazawa and Kitazawa, 2002; Chikatsu *et al.* 2000; Thomas *et al.* 1999]. As outlined, this leads to increased osteoclast differentiation; resulting bone resorption mobilizes growth factors, such as transforming growth factor beta (TGF- β), insulin-like growth factor, basic fibroblast growth factor and bone morphogenetic protein (BMP) from the bone matrix. Those cytokines in turn stimulate tumour proliferation and support tumour cell survival [Yin *et al.* 2005; Roodman, 2004; Kostenuik *et al.* 1992; Hauschka *et al.* 1986] (Figure 1).

The resulting vicious cycle is potentially inhibited by OPG, which leads to the development of compounds that inhibit the RANK/RANK-ligand pathway as therapeutic agents [Body *et al.* 2003].

As outlined in Figure 1, certain malignancies, such as prostate cancer and multiple myeloma, may produce RANK-ligand directly [Farrugia *et al.* 2003; Brown *et al.* 2001]. Furthermore, a RANK-ligand independent mechanism of osteoclast differentiation mediated by IL-1, IL-6, IL-8 and TNF- α exists [Bendre *et al.* 2005; Kudo *et al.* 2003], suggesting a potential mechanism of resistance to RANK-ligand inhibition.

RANK pathway in breast tumorigenesis

Recently, it was suggested that RANK-ligand may also have a direct role in breast cancer tumorigenesis. In a mouse model developed by Beleut and colleagues, adult ovariectomized mice were exposed to progesterone [Beleut *et al.* 2010]. In this model, progesterone drove the proliferation of mammary gland epithelial cells

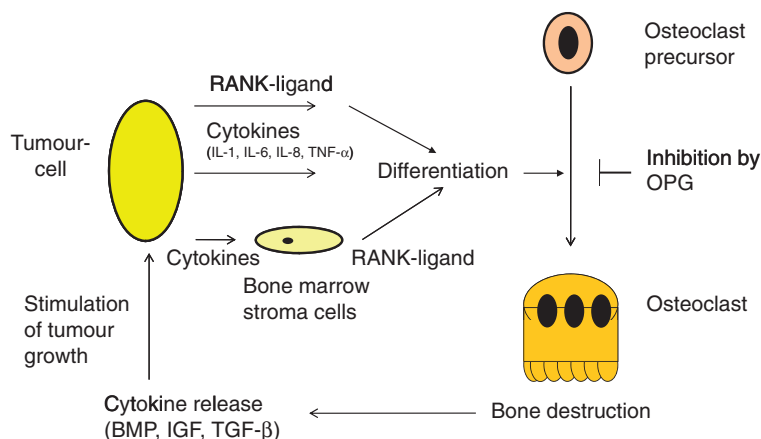


Figure 1. Vicious cycle of bone destruction. BMP, bone morphogenetic protein; IGF, insulin-like growth factor; IL, interleukin; OPG, osteoprotegerin; RANK-ligand, receptor activator of nuclear factor-kappaB ligand; TGF- β , transforming growth factor beta; TNF- α , tumour necrosis factor alpha.

(MECs) in two waves. A first, smaller wave of proliferation occurred in progesterone receptor (PR)-positive cells and was found to require cyclin D1. A second, larger wave, however, relied on RANK-ligand signalling.

Ablation of RANK in the mammary epithelium blocked progesterone-induced morphogenesis. On the other hand, systemic administration of RANK-ligand also triggered proliferation in the absence of PR signalling, and injection of recombinant OPG as a RANK signalling inhibitor blocked progesterone-induced proliferation [Beleut *et al.* 2010].

In line with these data, Schramek and colleagues showed that the administration of medroxyprogesterone acetate (MPA) triggered an induction of RANK-ligand in MECs. Results showed that inactivation of the RANK pathway in MECs prevented the expansion of a stem cell-enriched population in response to MPA and, furthermore, sensitized those cells to DNA damage-induced cell death. Consequently, deletion of RANK decreased incidence and delayed onset of MPA-driven mammary cancers [Schramek *et al.* 2010].

This data may offer a possible hypothesis for the induction of breast cancers by hormone replacement therapy with a combination of oestrogen and progestins and opens an opportunity for new approaches in breast cancer prevention.

Development of denosumab

Early development of drugs targeting RANK/RANK-ligand started with recombinant OPG (AMGN-0007). While OPG was active and well tolerated [Body *et al.* 2003; Bekker *et al.* 2001], AMG162, later named denosumab, a fully human antibody targeting RANK-ligand, reduced levels of bone turnover markers to a greater extent [Bekker *et al.* 2004].

In patients with osteoporosis, the effects of denosumab on levels of bone turnover markers were sustained for up to 6 months, enabling an administration schedule similar to that for intravenous bisphosphonates [Bekker *et al.* 2004]. Further studies were conducted in patients with bone metastases from solid cancers and multiple myeloma. Importantly, neither antibodies against denosumab nor any drug-related serious adverse events were observed [Body *et al.* 2006].

Phase II clinical trials of denosumab in malignancies and CTIBL

Two randomized phase II studies of denosumab in advanced cancer patients were initiated based upon those results. One trial included 255 bisphosphonate-naïve patients with metastatic breast cancer. Patients were randomly assigned to different doses and schedules of denosumab or a control group receiving zoledronic acid. Reduction of uNTX/Cr was defined as a primary study endpoint. Overall, denosumab and zoledronic acid yielded similar results and denosumab at 120 mg administered every 4 weeks was identified as the optimal schedule for further investigations. Serious adverse events were observed less frequently in patients treated with denosumab compared with the bisphosphonate group (9% *vs.* 16%) [Lipton *et al.* 2007].

A second randomized phase II study included patients already receiving various bisphosphonates (i.e. ibandronate, pamidronate and zoledronic acid) for bone metastases of solid cancers and multiple myeloma. It consisted of 111 patients with intermediate-to-high levels of uNTX at baseline randomized to denosumab or continuation of bisphosphonates. The percentage of patients reaching uNTX levels of more than 50 nmol/L at week 13 was defined as the primary study endpoint. This endpoint was met by 71% of patients in the denosumab group compared with 29% of patients who continued on bisphosphonates ($p < 0.001$). Adverse events were comparable between both groups [Fizazi *et al.* 2009]. When considering this trial, however, it is important to understand that the patients included were resistant to bisphosphonates as evidenced by intermediate-to-high baseline uNTX; it is not entirely clear whether results can be transferred to a general population.

The role of denosumab for the prevention of CTIBL was evaluated in another phase II trial: 252 patients with early breast cancer and reduced bone mass who received aromatase inhibitors in the adjuvant setting were included and randomized to denosumab 60 mg or placebo every 6 months. In the denosumab group, bone mineral density increased significantly over time (5.5% and 7.6%, at 12 and 24 months, respectively; $p < 0.0001$ [both time points]). Again, treatment was generally well tolerated and adverse events were similar between the respective denosumab and placebo groups [Ellis *et al.* 2008].

Denosumab for the treatment of bone metastases: results from phase III clinical trials

Recently, results of the first phase III trial to compare directly denosumab to zoledronic acid in patients with metastatic breast cancer patients were published (Amgen 20050136 [ClinicalTrials.gov identifier: NCT00321464]). A total of 2046 bisphosphonate-naïve patients (except treatment with oral bisphosphonates for osteoporosis) were included and randomized to denosumab 120 mg or zoledronic acid 4 mg every 4 weeks in a randomized, double-blind, active-controlled trial. Primary study endpoint was time to first on-study SRE (noninferiority); secondary endpoints consisted of time to first on-study SRE (superiority) and time to first and subsequent on-study SREs. In the denosumab group, a significant delay in time to first on-study SRE was observed (hazard ratio [HR] 0.82; 95% confidence interval [CI] 0.71–0.95; $p < 0.001$ noninferiority; $p = 0.01$ superiority). Indeed, median time to first on-study SRE was 26.4 months in patients receiving zoledronic acid, and was not reached in the denosumab group [Stopeck *et al.* 2010b]. This was recently updated at the 2010 San Antonio Breast Cancer Symposium where a median time to first on-study SRE of 32.4 months was reported in the denosumab group [Stopeck *et al.* 2010c]. Furthermore, denosumab reduced the risk of experiencing multiple SREs (analysis of time to first and subsequent on-study SRE) significantly (HR 0.77; 95% CI 0.66–0.89; $p = 0.001$) [Stopeck *et al.* 2010b]. The results are summarized in Table 1.

Bisphosphonates are known to have considerable activity on control and palliation of pain

associated with bone metastases [Kretschmar *et al.* 2007]. In a separate analysis evaluating the respective effects of zoledronic acid and denosumab on pain in all patients included in Amgen 20050136, a similar time to pain improvement was observed in both treatment arms. Patients with a baseline score of no/mild pain had a significantly longer median time to development of moderate/severe pain when treated with denosumab compared with zoledronic acid [Stopeck *et al.* 2010a].

Rates of severe (defined as Common Terminology Criteria of Adverse Events grade ≥ 3) and serious adverse events (e.g. life threatening or requiring hospitalization) once again were similar between both treatment groups. In general, those adverse events were mainly attributable to concomitant anticancer therapies. As expected, significantly more cases of pyrexia, bone pain, arthralgia and renal failure were observed in the zoledronic acid group, while hypocalcaemia and toothache, not associated with the development of osteonecrosis of the jaw (ONJ), were seen more often in patients receiving denosumab. Importantly, the overall rate of ONJs, defined as exposed necrotic bone that persists for at least 8 weeks [Cartsos *et al.* 2008], was similar in the respective treatment groups. Furthermore, known risk factors for ONJ, such as prior dental extractions and poor oral hygiene, were present in the vast majority of all ONJ cases [Stopeck *et al.* 2010b].

Another phase III trial was conducted in a mixed population of patients with different advanced solid cancers (excluding prostate and breast

Table 1. Comparison of denosumab vs. zoledronic acid in metastatic breast cancer ($n = 2046$).

Endpoint	HR	95% CI	<i>p</i> value
Primary endpoint			
Time to first on-study SRE (noninferiority)	0.82	0.71-0.95	>0.0001
Secondary endpoints			
Time to first on-study SRE (superiority)	0.82	0.71-0.95	0.01
Time to first and subsequent on-study SRE	0.77	0.66-0.89	0.001
Exploratory endpoints			
Overall disease progression	1.00	0.89-1.11	NS
Overall survival	0.95	0.81-1.11	NS
Skeletal morbidity rate (mean) (number of SREs per year)	D: 0.45; ZA: 0.58		0.004

CI, confidence interval; D, denosumab; HR, hazard ratio; NS, not significant; SRE, skeletal-related event (i.e. pathologic fracture, irradiation to bone, surgery to bone, spinal cord compression); ZA, zoledronic acid.

cancer) and multiple myeloma. Similar to NCT00321464, the primary study endpoint, noninferiority to zoledronic acid, was met (HR 0.84; 95% CI 0.71–0.98; $p=0.0007$), although a superiority of denosumab was not established [Henry *et al.* 2011].

Finally, another phase III trial of denosumab *versus* zoledronic acid was conducted in men with castration-resistant prostate cancer [ClinicalTrials.gov identifier: NCT00321620]. Overall, 1904 patients with bone metastases, all naïve for intravenous bisphosphonates were included. Again, time to first on-study SRE was chosen as the primary study endpoint. In patients receiving denosumab, median time to first on-study SRE was 20.7 months compared with 17.1 months in the zoledronic acid group (HR 0.82; 95% CI 0.71–0.95; $p<0.001$ noninferiority; $p=0.008$ superiority). In line with the aforementioned studies, the overall rate of serious adverse events was similar (63% *vs.* 60%), while once again a numerical increase in the rate of ONJ was observed in patients receiving denosumab (22 [2%] *vs.* 12 [1%]; $p=0.09$) [Fizazi *et al.* 2011].

Trials of denosumab in CTIBL

As outlined, bisphosphonates are active in the prevention of CTIBL [Van Poznak *et al.* 2010; Gnant *et al.* 2007]. It is still not proven, however, whether this effect eventually translates into a reduction in fracture rates [Valachis *et al.* 2010]. Denosumab, on the other hand, was found to lower the rate of vertebral fractures significantly in patients on androgen-deprivation therapy for prostate cancer [Smith *et al.* 2009]. Further studies are currently ongoing: the Austrian Breast and Colorectal Cancer Study Group Study 18 (ABCSG-18) randomized postmenopausal patients treated with aromatase inhibitors as adjuvant therapy for hormone receptor-positive early breast cancer to denosumab or placebo. This study is among the first phase III trials evaluating denosumab in the prevention of CTIBL in breast cancer and also includes relevant oncological treatment goals as secondary endpoints [ClinicalTrials.gov identifier: NCT00556374].

Clinical antitumour efficacy of bisphosphonates and denosumab

Preclinical data suggested a direct antitumour effect of zoledronic acid. Among other

mechanisms, synergistic activity of bisphosphonates in combination with chemotherapy, immunomodulatory properties as well as an anti-angiogenic effect were proposed [Neville-Webbe and Coleman, 2010]. While there is some clinical data in support of these assumptions, there is no clear-cut evidence yet. The ABCSG-12 study randomized premenopausal patients receiving adjuvant endocrine therapy to additive treatment with zoledronic acid or control. A significant reduction of breast cancer recurrence events was observed in the bisphosphonate group [Gnant *et al.* 2009].

In the postmenopausal bone protection trial (ZO-FAST [ClinicalTrials.gov identifier: NCT00171314]), early breast cancer patients on letrozole were randomly assigned to a group that received upfront zoledronic acid or a group that received bisphosphonates only when a drop in bone mineral density was observed [Eidtmann *et al.* 2010]. In support of ABCSG-12 results, significantly fewer recurrences occurred in the upfront group (HR 0.59; 95% CI 0.38–0.92; $p=0.0176$). In the smaller ZO-FAST study, however, no significant difference between both groups was observed [Brufsky *et al.* 2009]. EZO-FAST even found a nonsignificantly increased recurrence risk with immediate bisphosphonate administration [Coleman *et al.* 2009]. A combined analysis of those study results could not be performed as the Gail-Simon test was statistically significant for a quantitative interaction between the studies ($p=0.047$) [Coleman *et al.* 2009].

The AZURE trial (BIG 01/04; chemotherapy and/or hormone therapy with or without zoledronate in women with stage II or stage III breast cancer [ClinicalTrials.gov identifier: NCT00072020]) was the most recent of adjuvant bisphosphonates studies to report results [Coleman *et al.* 2010]. In contrast to ABCSG-12, addition of zoledronic acid caused no reduction in recurrence-free survival events in 3360 patients randomized to receive (neo) adjuvant chemotherapy and/or endocrine therapy with or without zoledronic acid (377 disease-free survival events with zoledronic acid, 375 in the control group; HR 0.98; 95% CI 0.85–1.13; $p=0.79$). Therefore, the exact role of bisphosphonates in the prevention of breast cancer recurrences awaits further clarification. Table 2 outlines the different results in terms of recurrence risk in the respective trials.

As for denosumab, there are currently no clinical data concerning a direct antitumour effect, although preclinical studies implicate a considerable role for the RANK/RANK-ligand pathway in breast cancer tumorigenesis [Beleut *et al.* 2010; Schramek *et al.* 2010]. As mentioned, ABCSG-18 evaluates the role of denosumab in the prevention of CTIBL [ClinicalTrials.gov identifier: NCT00556374]. Here, recurrence-free survival is assessed as a secondary endpoint. Another ongoing phase III trial, D-CARE (study of denosumab as adjuvant treatment for women with high-risk early breast cancer receiving neo-adjuvant or adjuvant therapy [ClinicalTrials.gov identifier: NCT01077154]) even defined bone metastasis-free survival as the primary study endpoint. Results are eagerly awaited, as these trials will yield important information concerning a potential role of denosumab in the prevention of breast cancer recurrences.

Side effects

Denosumab was generally well tolerated in several clinical trials conducted in advanced cancer patients. As RANK-ligand was identified as a costimulatory cytokine for T-cell activation, a higher risk for infectious diseases was anticipated [Wong *et al.* 1997]. Preclinical studies, however, revealed no increased risk of bacterial infections [Stolina *et al.* 2003], or altered virus clearance in response to influenza infections *in vivo* [Miller *et al.* 2007]. Importantly, in the aforementioned phase III study comparing denosumab to zoledronic acid in metastatic breast cancer, there was no increase in the number of infectious

adverse events (48.8% zoledronic acid *vs.* 46.4% denosumab) or infectious serious adverse events (8.2% zoledronic acid *vs.* 7.0% denosumab). In contrast, a meta-analysis of nine randomized controlled trials involving 10,329 participants with postmenopausal osteoporosis, early breast cancer and rheumatoid arthritis, identified a significant increase in the risk of serious infection in patients receiving denosumab (odds ratio 4.45; 95% CI 1.15–17.14; $p = 0.03$) [Anastasilakis *et al.* 2009].

The FREEDOM study [ClinicalTrials.gov identifier: NCT00089791; Cummings *et al.* 2009], a large randomized study including more than 7000 patients with osteoporosis, however, yielded different results: no increase in the risk of infections was observed in the denosumab group. Furthermore, the risk for developing cancer was not increased. This is of considerable importance, as denosumab might bind to a TNF-related apoptosis-inducing ligand, thereby increasing tumour cell survival. Therefore, at the moment, there is no clear signal that the risk for serious infections is increased with denosumab treatment.

In studies of denosumab in osteoporosis, no cases of ONJ were observed. Therefore, a lower incidence of ONJ was anticipated also in metastatic cancer patients. Results from three phase III clinical trials including 5677 patients with bone metastases, however, clearly indicated a risk of ONJ associated with denosumab treatment similar to that with bisphosphonates: 37 (1.3%) cases

Table 2. Randomized trials of zoledronic acid in early breast cancer.

Study	Number	Design	HR	Comment
ABCSG-12	1803	Premenopausal	HR 0.64; 95% CI 0.46–0.91; $p = 0.01$	Significantly fewer recurrences in ET +/- ZA patients receiving ZA
Z-FAST	602	Postmenopausal	HR 0.80; 95% CI 0.45–1.41; NS	Trend towards fewer recurrences in ET + early <i>vs.</i> delayed ZA patients treated with ZA
ZO-FAST	1065	Postmenopausal	HR 0.59; 95% CI 0.38–0.92; $p = 0.0176$	Significantly fewer recurrences in ET + early <i>vs.</i> delayed ZA patients receiving ZA
E-ZO-FAST	527	Postmenopausal	HR 1.76; 95% CI 0.83–3.69; NS	Trend towards more recurrences in ET + early <i>vs.</i> delayed ZA patients treated with ZA
AZURE	3360	Pre/postmenopausal	HR 0.98; 95% CI 0.85–1.13; NS	No effect of ZA in addition to standard CT and/or ET +/- ZA therapy

CI, confidence interval; CT, chemotherapy; ET, endocrine therapy; HR, hazard ratio; NS, not significant; ZA, zoledronic acid. See text for explanation of study name acronyms.

Table 3. Major differences between denosumab and zoledronic acid.

	Denosumab	Zoledronic acid
Type of substance	Monoclonal antibody	Chemical agent
Mode of action	Inhibition of osteoclast differentiation	Induction of osteoclast apoptosis
Application	Subcutaneous	Intravenous
Direct antitumour effect	Possible, not yet observed	Suggested from preclinical and inconsistent clinical data
Inhibition of T-cell function	Suggested from <i>in vitro</i> data; increased infection rate not fully excluded	Not observed
Osteonecrosis of the jaw	Relevant side effect in patients receiving denosumab for bone metastases. Not observed in patients treated for osteoporosis	Relevant side effect in patients receiving zoledronic acid for bone metastases and osteoporosis
Renal toxicity	Not observed	Relevant side effects

were recorded in patients treated with zoledronic acid compared with 52 (1.8%) cases in patients receiving denosumab [Brown *et al.* 2010]. Recently, Van den Wyngaert and colleagues reported pooled ONJ safety data from all three randomized phase III trials. A total of 89 ONJ cases were reported with 52 (1.83%; 95% CI 1.37–2.39) occurring in the denosumab group and 37 (1.30%; 95% CI 0.92–1.79) in the zoledronic acid group, respectively. Overall, there was no significant difference in the pooled risk ratio (RR) for ONJ (RR 1.40; 95% CI 0.92–2.13; $p = 0.11$). It is necessary to remember, however, that neither separately nor pooled, those trials had adequate statistical power (>80%) to detect an excess relative risk of ONJ [Van den Wyngaert *et al.* 2011]. Therefore, postmarketing risk-benefit studies focusing on incidence of ONJ appear warranted.

Renal toxicity is another side effect associated with bisphosphonates. In AMG20050136, renal toxicity (defined as increased blood creatinine and blood urea, oliguria, renal impairment, proteinuria, decreased creatinine clearance, acute renal failure and chronic renal failure) was more frequently observed with zoledronic acid, especially in patients with baseline clearance of ≤ 60 ml/min. Therefore, denosumab represents a valid therapeutic option for patients with bone metastases suffering from chronic renal failure [Stopeck *et al.* 2010b].

Major differences between zoledronic acid and denosumab are summarized in Table 3.

Conclusion

Bisphosphonates are currently the standard of care for the treatment of bone metastases in

patients with advanced breast cancer, as these drugs were shown to reduce effectively the number of SREs. However, SREs might occur despite therapy, highlighting the need for alternative treatment approaches.

Derangement of the balance in the RANK/RANK-ligand/OPG pathway is a major driving force in the development of malignant bone lesions. Denosumab is a fully human antibody blocking RANK-ligand, thereby interfering with the vicious cycle of bone destruction. Clinical studies suggest at least similar efficacy as zoledronic acid, with one large prospectively randomized phase III trial also showing superiority of denosumab *versus* zoledronic acid in terms of delaying SREs in advanced breast cancer. Overall, denosumab was well tolerated, with generally mild side effects observed. However, an increased risk for infectious disease cannot fully be excluded, the risk for developing ONJs was similar to bisphosphonates; therefore, the same safety recommendations apply for this condition. Moreover, preclinical studies also suggest an important role for the RANK/RANK-ligand pathway in breast tumorigenesis. Thus, ongoing clinical studies are evaluating the effect of denosumab on CTIBL and also breast cancer recurrences in the adjuvant setting.

In conclusion, data from clinical trials of denosumab in bone metastases from solid tumours in general and from breast cancer in particular seriously challenge the current standard of care for these conditions, which is the use of bisphosphonates. Based on the published results of phase III clinical trials aiming at the delay of SREs in patients with bone metastases from solid tumours, denosumab has already been licensed

by the US Food and Drug Administration for the prevention of SREs in patients with bone metastases from solid tumours including breast cancer (XGEVA^R) in the USA. In Europe, the data have been filed with the European Medicines Agency and the decision is expected in the third quarter of 2011.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

G.Steger: fees for lectures and advisory boards from Amgen and Novartis. R.Bartsch: lecture fees from Novartis.

References

- American Cancer Society. (2009) Facts and figures. [http://www.cancer.org/docroot/STT/STT_0.asp; last accessed 6 February 2011].
- Amir, E., Ocaña, A., Seruga, B., Josse, R. and Clemons, M. (2010) Medical oncology: Zoledronic acid for breast cancer therapy-induced bone loss. *Nat Rev Clin Oncol* 7: 187–188.
- Anastasilakis, A.D., Toulis, K.A., Goulis, D.G., Polyzos, S.A., Delaroudis, S., Giomisi, A. *et al.* (2009) Efficacy and safety of denosumab in postmenopausal women with osteopenia or osteoporosis: A systematic review and a meta-analysis. *Horm Metab Res* 41: 721–729.
- Baron, R., Ferrari, S. and Russell, C. (2011) Denosumab and bisphosphonates: Different mechanisms of action and effect. *Bone* 48: 677–692.
- Bartsch, R. and Steger, G.G. (2009) Role of denosumab in breast cancer. *Expert Opin Biol Ther* 9: 1225–1233.
- Bekker, P.J., Holloway, D., Nakanishi, A., Arrighi, M., Leese, P.T. and Dunstan, C.R. (2001) The effect of a single dose of osteoprotegerin in postmenopausal women. *J Bone Miner Res* 16: 348–360.
- Bekker, P.J., Holloway, D.L., Rasmussen, A.S., Murphy, R., Martin, S.W., Leese, P.T. *et al.* (2004) A single-dose placebo-controlled study of AMG 162, a fully human monoclonal antibody to RANKL, in postmenopausal women. *J Bone Miner Res* 19: 1059–1066.
- Beleut, M., Rajaram, R.D., Caikovski, M., Ayyanan, A., Germano, D., Choi, Y. *et al.* (2010) Two distinct mechanisms underlie progesterone-induced proliferation in the mammary gland. *Proc Natl Acad Sci U S A* 107: 2989–2994.
- Bendre, M.S., Margulies, A.G., Walser, B., Akel, N.S., Bhattacharya, S., Skinner, R.A. *et al.* (2005) Tumour derived interleukin-8 stimulates osteolysis independent of the receptor activator of nuclear factor-kappa B ligand pathway. *Cancer Res* 65: 11001–11009.
- Body, J.J., Facon, T., Coleman, R.E., Lipton, A., Geurs, F., Fan, M. *et al.* (2006) A study of the biological receptor activator of nuclear factor-kappa B ligand inhibitor, denosumab, in patients with multiple myeloma or bone metastases from breast cancer. *Clin Cancer Res* 12: 1221–1228.
- Body, J.J., Greipp, P., Coleman, R.E., Facon, T., Geurs, F., Ferman, J.P. *et al.* (2003) A phase I study of AMG-0007 a recombinant osteoprotegerin construct, in patients with multiple myeloma or breast carcinoma related bone metastases. *Cancer* 97: 887–892.
- Brown, J.E., Barrios, C.H., Diel, I.J., Facon, T., Fizazi, K., Ibrahim, T. *et al.* (2010) Incidence and outcomes of osteonecrosis of the jaw from an integrated analysis of three pivotal randomized double-blind, double-dummy phase 3 trials comparing denosumab and zoledronic acid for treatment of bone metastases in advanced cancer patients or myeloma. In: *10th International Conference on Cancer-induced Bone Disease, OC-15*, Sheffield 22–25 September 2010.
- Brown, J.E., Thomson, C.S., Ellis, S.P., Gutcher, S.A., Purohit, O.P. and Coleman, R.E. (2003) Bone resorption predicts for skeletal complications in metastatic bone disease. *Br J Cancer* 89: 2031–2037.
- Brown, J.M., Corey, E., Lee, Z.D., True, L.D., Yun, T.J., Tondravi, M. *et al.* (2001) Osteoprotegerin and RANK ligand expression in prostate cancer. *Urology* 57: 611–616.
- Brufsky, A.M., Bossermann, L.D., Caradonna, R.R., Haley, B.B., Jones, C.M., Moore, H.C. *et al.* (2009) Zoledronic acid effectively prevents aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole: Z-FAST study 36 months follow-up results. *Clin Breast Cancer* 9: 77–85.
- Cartsos, V.M., Zhu, S. and Zavras, A.I. (2008) Bisphosphonate use and the risk of adverse jaw outcomes. *J Am Dent Assoc* 139: 23–30.
- Chikatsu, N., Takeuchi, Y., Tamura, Y., Fukumoto, S., Yano, K., Tsuda, E. *et al.* (2000) Interactions between cancer and bone marrow cells induce osteoclast differentiation factor expression and osteoclast-like cell formation. *in vitro. Biochem Biophys Res Comm* 267: 632–637.
- Coleman, R., Bundred, N., De Boer, R., Llombarto, A., Campbell, I., Neven, P. *et al.* (2009) Impact of zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: Z-FAST, ZO-FAST, and E-ZO-FAST. *Cancer Res* 69: 733s.
- Coleman, R.E. (2001) Metastatic bone disease: Clinical features, pathophysiology, and treatment strategies. *Cancer Treat Rev* 27: 165–176.

- Coleman, R.E., Thorpe, H.C., Cameron, D., Dodwell, D., Burkinshaw, R., Keane, M. *et al.* (2010) Adjuvant treatment with zoledronic acid in stage II/III breast cancer. The AZURE Trial (BIG 01/04). In: *33rd Annual San Antonio Breast Cancer Symposium (SABCS)*, Abstract S4–S5.
- Cummings, S.R., San Martin, J., McClung, M.R., Siris, E.S., Eastell, R., Reid, I.R. *et al.* (2009) Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med* 361: 756–765.
- Eastell, R., Hannon, R.A., Cuzick, J., Dowsett, M., Clack, G. and Adams, J.E. (2006) 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* 21: 1215–1223.
- Eidtmann, H., de Boer, R., Bundred, N., Llombart-Cussac, A., Davidson, N., Neven, P. *et al.* (2010) Efficacy of zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: 36-month results of the ZO-FAST Study. *Ann Oncol*, doi: 10.1093/annonc/mdq217 [Epub ahead of print].
- Ellis, G.K., Bone, H.G., Chlebowski, R., Paul, D., Spadafora, S., Fan, M. *et al.* (2008) Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for nonmetastatic breast cancer. *J Clin Oncol* 26: 4875–4882.
- Farrugia, A.N., Atkins, G.J., To, L.B., Pan, B., Horvath, N., Kostakis, P. *et al.* (2003) Receptor activator of nuclear factor- κ B ligand expression by human myeloma cells mediates osteoclast formation *in vitro* and correlates with bone destruction *in vivo*. *Cancer Res* 63: 5438–5445.
- Fizazi, K., Carducci, M., Smith, M., Damião, R., Brown, J., Karsh, L. *et al.* (2011) Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: A randomised, double-blind study. *Lancet* 377: 813–822.
- Fizazi, K., Lipton, A., Mariette, X., Body, J.J., Rahim, Y., Gralow, J.R. *et al.* (2009) Randomized phase II trial of denosumab in patients with bone metastases from prostate cancer, breast cancer, or other neoplasms after intravenous bisphosphonates. *J Clin Oncol* 27: 1564–1571.
- Frith, J.C., Mönkkönen, J., Auriola, S., Mönkkönen, H. and Rogers, M.J. (2001) The molecular mechanism of action of the antiresorptive and antiinflammatory drug clodronate: Evidence for the formation *in vivo* of a metabolite that inhibits bone resorption and causes osteoclast and macrophage apoptosis. *Arthritis Rheum* 44: 2201–2210.
- Geusens, P. (2009) Emerging treatments for postmenopausal osteoporosis – focus on denosumab. *Clin Interv Aging* 4: 241–250.
- Giuliano, N., Colla, S. and Rizzoli, V. (2004) Update on the pathogenesis of osteolysis in multiple myeloma patients. *Acta Biomed* 75: 143–152.
- Gnant, M.F., Mlineritsch, B., Luschin-Ebengreuth, G., Grampp, S., Kaessmann, H., Schmid, M. *et al.* (2007) 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* 25: 820–828.
- Gnant, M., Mlineritsch, B., Schippinger, W., Luschin-Ebengreuth, G., Pöstlberger, S., Menzel, C. *et al.* (2009) Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *N Engl J Med* 360: 679–691.
- Hauschka, P.V., Mavrakos, A.E., Iafrati, M.D., Doleman, S.E. and Klagsbrun, M. (1986) Growth factors in bone matrix. Isolation of multiple types by affinity chromatography on heparin-sepharose. *J Biol Chem* 261: 12665–12674.
- Henry, D.H., Costa, L., Goldwasser, F., Hirsh, V., Hungria, V., Prausova, J. *et al.* (2011) 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* 29: 1125–1132.
- Hines, S.L., Mincey, B.A., Sloan, J.A., Thomas, S.P., Chottiner, E., Loprinzi, C.L. *et al.* (2009) Phase III randomized, placebo-controlled, double-blind trial of risenedronate for the prevention of bone loss in premenopausal women undergoing chemotherapy for primary breast cancer. *J Clin Oncol* 27: 1047–1053.
- Howell, A., Cuzick, J., Baum, M., Buzdar, A., Dowsett, M., Forbes, J.F. *et al.* (2005) Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 365: 60–62.
- Kanis, J.A., Delmas, P., Burckhardt, P., Cooper, C. and Torgerson, D. (2007) Guidelines for diagnosis and management of osteoporosis. The European Foundation for Osteoporosis and Bone Disease. *Osteoporos Int* 7: 390–406.
- Kitazawa, S. and Kitazawa, R. (2002) RANK ligand is a prerequisite for cancer-associated osteolytic lesions. *J Pathol* 198: 228–236.
- Kostenuik, P.J., Singh, G., Suyama, K.L. and Orr, F.W. (1992) A quantitative model for spontaneous bone metastasis: Evidence for a mitogenic effect of bone on Walker 256 cancer cells. *Clin Exp Metastasis* 10: 403–410.
- Kretschmar, A., Wiege, T., Al-Batran, S.E., Hinrichs, H.F., Kindler, M., Steck, T. *et al.* (2007) Rapid and sustained influence of intravenous zoledronic acid on course of pain and analgesics consumption in patients with cancer with bone metastases: A multicenter open-label study over 1 year. *Support Cancer Ther* 4: 203–210.

- Kudo, O., Sabokbar, A., Pockok, A., Itonaga, I., Fujikawa, Y. and Athanasou, N.A. (2003) Interleukin-6 and Interleukin-11 support human osteoclast formation by a RANKL-independent mechanism. *Bone* 32: 1–7.
- Lipton, A., Steger, G.G., Figueroa, J., Alvarado, C., Solal-Celigny, P., Body, J.J. *et al.* (2007) Randomized active-controlled phase II study of denosumab efficacy and safety in patients with breast cancer-related bone metastases. *J Clin Oncol* 25: 4431–4437.
- Luckman, S.P., Hughes, D.E., Coxon, F.P., Graham, R., Russell, G. and Rogers, M.J. (1998) Nitrogen-containing bisphosphonates inhibit the mevalonate pathway and prevent post-translational prenylation of GTP-binding proteins, including Ras. *J Bone Miner Res* 13: 581–589.
- Miller, R.E., Branstetter, D., Armstrong, A., Kennedy, B., Jones, J., Cowan, L. *et al.* (2007) Receptor activator of NF- κ B ligand inhibition suppresses bone resorption and hypercalcemia but does not affect host immune response to influenza infection. *J Immunol* 179: 266–274.
- Mundy, G.R. (2001) Metastasis to bone: Causes, consequences and therapeutic opportunities. *Nat Rev Cancer* 2: 584–593.
- Neville-Webbe, H.L. and Coleman, R.E. (2010) Bisphosphonates and RANK ligand inhibitors for the treatment and prevention of metastatic bone disease. *Eur J Cancer* 46: 1211–1222.
- Perez, E.A., Josse, R.G., Pritchard, K.I., Ingle, J.N., Martino, S., Findlay, B.P. *et al.* (2006) Effect of letrozol *versus* placebo on bone mineral density in women with primary breast cancer completing 5 or more years of adjuvant tamoxifen: A comparison study to NCIC CTC MA.17. *J Clin Oncol* 24: 3629–3635.
- Rodan, G.A. and Martin, T.J. (1981) Role of osteoblasts in hormonal control of bone resorption: A hypothesis. *Calcif Tissue Int* 33: 349–351.
- Roodman, G.D. (2004) Mechanisms of bone metastases. *N Engl J Med* 350: 1655–1664.
- Ross, J.R., Saunders, Y., Edmonds, P.M., Patel, S., Broadley, K.E. and Johnston, S.R. (2003) Systematic review of the role of bisphosphonates on skeletal morbidity in metastatic breast cancer. *BMJ* 327: 469–474.
- Schramek, D., Leibbrandt, A., Sigl, V., Kenner, L., Pospisilik, J.A., Lee, H.J. *et al.* (2010) Osteoclast differentiation factor RANKL controls development of progesterin-driven mammary cancer. *Nature* 468: 98–102.
- Smith, M.R., Egerdie, B., Hernández Toriz, N., Feldman, R., Tammela, T.L., Saad, F. *et al.* (2009) Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *N Engl J Med* 361: 7445–7455.
- Stolina, M., Guo, J., Faggioni, R., Brown, H. and Senaldi, G. (2003) Regulatory effects of osteoprotegerin on cellular and humoral immune responses. *Clin Immunol* 109: 347–354.
- Stopeck, A., Fallowfield, L., Patrick, D., Cleeland, C.S., De Boer, R.H., Steger, G.G. *et al.* (2010a) Effect of denosumab *versus* zoledronic acid (ZA) on pain in patients (pts) with metastatic breast cancer: Results from a phase III clinical trial. *J Clin Oncol* 28(15), Abstract 1024.
- Stopeck, A.T., Lipton, A., Body, J.J., Steger, G.G., Tonkin, K., De Boer, R.H. *et al.* (2010b) 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* 28: 5132–5139.
- Stopeck, A., Martin, M., Ritchie, D., Body, J.J., Paterson, A., Viniegra, M. *et al.* (2010c) Effect of denosumab *versus* zoledronic acid treatment in patients with breast cancer and bone metastases: Results from the extended blinded treatment phase. *Cancer Res* 2010: P6-14-01.
- Thomas, R.J., Guise, T.A., Yin, J.J., Elliott, J., Horwood, N.J., Martin, T.J. *et al.* (1999) Breast cancer cells interact with osteoblasts to support osteoclast formation. *Endocrinology* 140: 4451–4458.
- Thürlimann, B., Keshaviah, A., Coates, A.S., Mouridsen, H., Mauriac, L., Forbes, J.F. *et al.* (2005) Breast International Group (BIG) 1-98 Collaborative Group. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. *N Engl J Med* 353: 2727–2757.
- Valachis, A., Polyzos, N.P., Gergoulis, V., Mavroudis, D. and Mauri, D. (2010) Lack of evidence for fracture prevention in early breast cancer bisphosphonate trials: A meta-analysis. *Gynecol Oncol* 117: 139–145.
- Van den Wyngaert, T., Wouters, K., Huizing, M.T. and Vermorken, J.B. (2011) RANK ligand inhibition in bone metastatic cancer and risk of osteonecrosis of the jaw (ONJ): Non bis in idem? *Support Care Cancer*, doi: 10.1007/s00520-010-1061-0 [Epub ahead of print].
- Van Poznak, C., Hannon, R.A., Mackey, J.R., Campone, M., Apffelstaedt, J.P., Clack, G. *et al.* (2010) Prevention of aromatase inhibitor-induced bone loss using risedronate: The SABRE trial. *J Clin Oncol* 28: 967–975.
- Vega, D., Maalouf, N.M. and Sakhaee, K. (2007) The role of receptor activator of nuclear factor-kappaB (RANK)/RANK ligand/osteoprotegerin: Clinical implications. *J Clin Endocrinol Metab* 92: 4514–4521.
- Wong BR, Rho J, Arron J, Robinson E, Orlinick J, Chao M, *et al.* (1997) TRANCE is a novel ligand of the tumor necrosis factor receptor family that activates c-Jun N-terminal kinase in T cells. *J Biol Chem* 272: 25190–25194.
- Yin, J.J., Pollock, C.B. and Kelly, K. (2005) Mechanisms of cancer metastasis to the bone. *Cell Res* 15: 57–62.