Denosumab in the treatment of bone metastasis from solid tumors

Amrallah A. Mohammmad[1, 2]; Abdullah Alzahran[1]; Hani El-Tanni[1]

(1) Oncology Center, King Abdullah Medical City - Holy Capital, Saudi Arabia
(2) Department of Medical Oncology, Faculty of Medicine, Zagazig University, Egypt

✉ *Corresponding Author: Dr Amrullah Abdel Moneim*
King Abdullah Medical City, Holly Capital
Saudi Arabia
Email: amrallaabdelmoneem@yahoo.com

Key words: Bone metastasis, denosumab.

ISSN: 2070-254X

Introduction

Bone is the most common site of metastatic disease in patients with solid tumors; it is the third common place for metastasis after lung and liver. Given the high prevalence of breast, prostate, and lung cancer, they are responsible for more than 80% of cases of metastatic bone disease. Patients with metastatic disease of the bone are at risk for skeletal-related events (SREs), which are defined as: pathologic fracture, spinal cord compression, and other complications related to skeletal involvement, including hypercalcemia of malignancy, radiation therapy to alleviate pain or prevent fracture or surgery to prevent or treat fracture. Thus SREs are a major source of morbidity for cancer patients and its prevention is a vital component of their oncologic care.

Since the 1990s, bisphosphonates have been the mainstay of treatment to prevent SREs in patients with cancer metastases to bone. They acting mainly through two ways: firstly by inhibiting continued bone resorption and secondly by induction of apoptosis (1).

Zoledronic acid is the first bisphosphonate approved for use in all solid tumor patients with bone metastases as well as in multiple myeloma. Despite optimal bisphosphonate therapy, 30%–50% of cancer patients with bone metastases still develop SREs while on bisphosphonate therapy (2, 3). In addition, there are concerning treatment-related side effects associated with its use, including gastrointestinal irritation, nephrotoxicity, osteonecrosis of the jaw (ONJ), and hypocalcaemia. Intravenous infusion of zoledronic acid can be associated with an acute-phase reaction, including bone pain, fever, and chills in up to 30% of patients as well as renal toxicity that is dose and infusion time dependent. It is not recommended for use in patients with a creatinine clearance lower than 30 mL/minute and with dose-modification if it is less than 60 mL/minute (4). consequently, monthly monitoring of renal function is required prior to each dose.

It is hypothesized that tumor cells in the bone lead to increased expression of receptor activator of nuclear factor kappa-B ligand (RANKL) on osteoblasts and their precursors. RANKL is an essential mediator of osteoclast function, formation, and survival (5-7). Excessive RANKL-induced osteoclast activity results in resorption and local bone destruction leading to SREs (8, 9).

The first available drug to target the RANK-RANKL pathway is denosumab, a fully human monoclonal antibody that specifically binds and neutralizes RANKL, thereby inhibiting osteoclast function. The initial Phase I trials demonstrated that osteoclastic activity is almost completely eradicated while denosumab is in circulation, however, the effect is reversible (10).

In the Phase III FREEDOM trial, 7868 postmenopausal women (aged 60–90 years) with osteoporosis were randomly assigned to subcutaneous denosumab (60 mg every 6 months) or placebo. After 3 years, denosumab improved bone mineral density compared with placebo and when compared with bisphosphonates; it has shown improvements in both bone mineral density and markers of bone loss (11).

The guidelines from the American Society of Clinical Oncology and the National Comprehensive Cancer Network recommend bone mineral density testing with a dual-emission x-ray absorptiometry scan for postmenopausal women taking aromatase inhibitors and drug therapy for those with documented osteoporosis (12).

In a randomized, double-blind, placebo-controlled trial, 252 women with hormone receptor-positive, early-stage breast cancer treated with adjuvant aromatase inhibitor therapy were randomly assigned to receive placebo or subcutaneous denosumab 60 mg every 6 months. At 12 and 24 months, lumbar spine bone mineral density increased by 5.5% and 7.6%, respectively, in the denosumab group compared with the placebo group (*P* , 0.0001) (13).

In the HALT (Hormone Ablation Bone Loss) trial, 1468 men receiving androgen deprivation therapy for non metastatic prostate cancer were randomly assigned to denosumab (60 mg subcutaneously every 6 months) or placebo. Eligibility included male gender, age 70 years or, 70 years with baseline low bone mineral density (T score at the lumbar spine, total hip, or femoral neck of less than -1.0). At 24 months, denosumab was associated with increased bone mineral density at all measured sites (*P*, 0.001 for all comparisons) (14). The promising outcomes in the initial trials with denosumab in treatment-related osteoporosis associated with breast and prostate cancer led to exploration of its use for the prevention of skeletal-related events in patients with solid tumors and bone metastasis.

Doses

Denosumab has US Food and Drug Administration (FDA) approval at a dose of 60 mg subcutaneously every 6 months for the treatment of both primary osteoporosis and bone loss associated with aromatase inhibitor therapy in early-stage breast cancer and androgen deprivation therapy for nonmetastatic prostate

cancer. At a dose of 120 mg subcutaneously every four weeks for the prevention of SREs in patients with bone metastases from solid tumors.

Pharmacokinetics and Side effects

Denosumab absorption is rapid and sustained, with a bioavailability of 62%, a steady-state mean serum concentration of 20.5 ug/mL, and an elimination half-life of 28 days. A decrease in bone resorption markers is observed within 24 hours after initial dose administration, and steady-state levels are achieved by 6 months following multiple doses at the 120 mg monthly schedule (15).

It is eliminated through the immunoglobulin clearance pathway via the reticuloendothelial system, is thus thought to be independent of renal or hepatic function (16). So no need to dose reduction or renal monitoring with denosumab therapy. However, there is a lack of safety data in patients with severe renal dysfunction because patients with creatinine clearance levels less than 30 mL/minute were excluded from the trials. No clear data about its use in patients with a creatinine clearance of less than 30 mL/minute or in those who are receiving dialysis. The risk of hypocalcaemia is increased with chronic renal disease. To minimize this risk, Healthcare Professionals reminded the following:

- Pre-existing hypocalcaemia must be corrected prior to initiating therapy.
- Supplementation of calcium and vitamin D is required in all patients unless hypercalcaemia is present.
- If hypocalcaemia occurs, additional calcium supplementation may be necessary.
- Patients with severe renal impairment (creatinine clearance < 30 ml/min) or receiving dialysis, calcium monitoring is recommended.

In the setting of osteoporosis, the FREEDOM (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months) trial is the largest single trial comparing denosumab with placebo for the prevention of fractures. In this study, there were no significant differences between the 3900 subjects who received denosumab and those who received placebo with regard to the total incidence of adverse events, serious adverse events, or discontinuation of study treatment because of adverse events, no increase in the risk of cancer or overall rate of infection, cardiovascular disease, delayed fracture healing, or hypocalcaemia, and there were no cases of ONJ (11).

Because RANKL is expressed on subsets of T and B cells, there is a theoretical possibility that denosumab may be immunosuppressive. RANKL-deficient mice lack normal lymph node development and have inhibition of early T and B lymphocyte development (17). However, in clinical trials, a statistically significant or clinically meaningful effect on the immune system has not been observed. In one trial, denosumab therapy had no significant effect on mean white blood cell counts, absolute lymphocyte counts, T and B cell counts, or immunoglobulins, and no meaningful difference was seen regarding incidence of infection (10). Phase II and III trials of denosumab for the treatment and prevention of osteoporosis suggested a slight increase in the rate of certain infectious complications, including cellulitis (18). However, the overall infection rate did not differ from placebo, and an association between denosumab and serious adverse infectious events has not been observed in any of the three large Phase III registration trials in cancer patients.

Disease-specific use

There have been three international Phase III randomized, double-blind, active controlled studies including over 5700 patients comparing denosumab with zoledronic acid for the prevention of SREs in patients with breast cancer, prostate cancer, and other solid tumors or multiple myeloma with bone metastases which led to FDA approval of denosumab for this indication.

The three trials had identical study designs. Patients were randomly assigned to receive either denosumab 120mg Q4W administered as a subcutaneous injection or zoledronic acid 4mg (adjusted for creatinine clearance) administered intravenously Q4W and the corresponding placebos. Patients had histologically or cytologically confirmed tumors and radiographic evidence of at least one bone metastasis. Patients were ineligible if they had received bisphosphonate treatment for bone metastasis or had previous ONJ, unhealed dental or oral surgery, ECOG status more than two, or creatinine clearance less than 30 ml/min. Supplementation with calcium and vitamin D was strongly recommended. All patients could continue to receive anticancer therapies. The primary endpoint was time to first SREs, with the study powered to detect noninferiority of denosumab versus zoledronic acid. Secondary endpoints included time to first on-study SRE (superiority test) and time to first and subsequent on-study SRE (multiple event analysis).

Breast cancer

In patients with breast cancer (n=2046), denosumab delayed the time to first on-study SRE by 18% compared with zoledronic acid (hazards ratio 0.82; 95% confidence interval 0.71–0.95; *P,* 0.001 for noninferiority, *P* = 0.01 for superiority). Median time to first SRE was 26.4 months in the zoledronic acid group and had not been reached in the denosumab group at the time of the primary analysis. With an additional 4 months of blinded treatment, the median time to first skeletal-related event was reached in the denosumab arm at 32.4 months (19). Denosumab also reduced the risk of subsequent SREs by 23% (risk ratio 0.77; 95% CI 0.66–0.89, P, 0.001). Overall survival and disease progression were similar between the two groups.

Adverse effects (AEs) were different between the two arms, including the incidence of flu-like symptoms (acute-phase reactions, 27.3% with zoledronic acid versus 10.4% with denosumab) and renal toxicity (8.5% with zoledronic acid versus 4.9% with denosumab). No patient treated with denosumab and 10 patients (1%) treated with zoledronic acid experienced serious adverse events associated with acute-phase reactions during the first 3 days after treatment. These events included pyrexia (n = 7), bone pain (n = 2), and asthenia, back pain, chest pain, chills, headache, and malaise (n = 1 each). Nine of the 10 patients in the zoledronic acid group with serious acute-phase reactions required hospitalization or prolongation of hospitalization (20).

AEs potentially associated with renal toxicity (8.5% *v* 4.9%; *P*=.001), especially severe (2.2% *v* 0.4%) and serious renal AEs (1.5% *v* 0.2%), occurred more frequently with zoledronic acid. The incidence of renal AEs among patients with baseline renal clearance ≤ 60 mL/ min was also higher in the zoledronic acid group (20.0%) than in the denosumab group (5.9%), and a greater proportion of patients had decreases in their baseline creatinine clearance from ≥ 60 mL/min to<60 mL/min with zoledronic acid (16.1%) compared with denosumab (12.7%). Expected decreases in serum calcium (which were generally mild and transient), phosphorus, and total alkaline phosphatase were observed in both groups. ONJ occurred infrequently (20 [2.0%] denosumab *v* 14 [1.4%] zoledronic acid) and the rates were not statistically significantly different between groups (*P*=.39), the

cumulative incidence in the denosumab and zoledronic acid groups, respectively, was 0.8% and 0.5% at 1 year, 1.9% and 1.2% at 2 years, and 2.0% and 1.4% at 3 years. Known risk factors for ONJ, including history of dental extraction, poor oral hygiene, or use of dental appliance occurred in 18 (90%) of 20 and 10 (71%) of 14 patients in denosumab and zoledronic acid groups, respectively. Fifteen (75%) denosumab-treated and 11 (79%) zoledronic acid-treated patients who developed ONJ were receiving or had received chemotherapy, and four (29%) patients in the zoledronic acid group (v zero in the denosumab group) had received prior oral bisphosphonate therapy for osteoporosis. Antiangiogenic therapy has also been associated with an increased risk of ONJ. Four (20%) ONJ events in the denosumab group and two (14%) in the zoledronic acid group occurred in patients receiving antiangiogenic therapy. As of 10 (50%) denosumab-treated patients and six (43%) zoledronic acid–treated patients had resolution of the ONJ event; 10 (50%) denosumab-treated patients and nine (64%) zoledronic acid–treated patients reported local infection; and seven patients in each group (35%, denosumab; 50%, zoledronic acid) reported undergoing limited surgical procedures such as debridement and sequestrectomy (21-23).

Patient-reported outcomes analyzed in the trial included pain using the Brief Pain Inventory and quality of life as assessed by the Functional Assessment of Cancer Therapy- General (FACT-G) score. 30 Patients were asked to complete the Brief Pain Inventory at baseline, day 8, and before each monthly visit through the end of study. In patients with scores of no/mild pain at baseline (n=1042), median time to development of moderate/severe pain with denosumab was 295 days compared with 176 days in those treated with zoledronic acid (HR 0.78, 95% CI 0.67–0.92, $P = 0.0024$). Time to pain improvement was similar between treatment arms (median 82 days for denosumab, median 85 days for zoledronic acid; HR 1.02, 95% CI 0.91–1.15, $P = 0.7245$). Similarly, health-related quality of life was higher in the denosumab arm than in the zoledronic acid arm throughout the study as well as improvements in emotional and physical state (24).

Prostate cancer

The Phase III trial in prostate cancer randomized 1904 patients with metastatic castrate-resistant prostate cancer to either denosumab or zoledronic acid treatment using an identical double-blind, active-controlled design. Patients with bone metastases from prostate cancer and high urinary NTx levels have an increased risk of SREs, time to a first SRE, disease progression, and death (25, 26).

Denosumab delayed the time to a first SRE by 18% (a median of 3.6 months) compared with zoledronic acid (hazard ratio=0.82, 95% CI, 0.71–0.95; P=0.0002 for noninferiority and P=0.008 for superiority). Also it delayed the time to multiple SREs, reducing the risk by 18% (rate ratio=0.82, 95% CI, 0.71–0.94, P=0.008). Overall survival, disease progression and median prostate-specific antigen levels were similar between the treatment groups throughout the study. At week 13, the decrease in urinary NTx/ creatinine was significantly greater in the denosumab group (median decrease of 84% in the denosumab group vs 69% in the zoledronic acid group, P, 0.0001). Overall, occurrences of AEs were similar between the groups. Hypocalcaemia was more common in the denosumab group with no fetal episodes (13% in the denosumab group versus 6% in the zoledronic acid group, P, 0.0001). The cumulative rate of ONJ between the two groups was not statistically significant, occurring in 1% (12 patients) in the zoledronic acid group versus 2% (22 patients) in the denosumab group. AEs associated with acute-phase reactions occurred in 8% of patients on denosumab and 18% of patients on zoledronic acid. Adverse events related to renal impairment were similar between the two groups, at 15% in the denosumab group and 16% in the zoledronic acid group. However, the zoledronic acid group required more frequent dose adjustment / holding for renal dysfunction.

Solid tumors other than breast and prostate cancer

The third Phase III trial of denosumab in the setting of metastatic disease was carried out in 1776 patients with multiple myeloma or solid tumors other than breast or prostate cancer with at least one bone metastasis or osteolytic lesion. The design was identical to that of the other two Phase III trials described previously. Approximately 40% of enrolled patients had non-small cell lung cancer and 10% had multiple myeloma. Only 20% of patients remained on study, with the majority of patients discontinuing therapy as a result of death (35%), withdrawal of consent (15%), or disease progression (13%). This trial had the shortest median time on study at approximately 7 months in both treatment groups (27).

The median time to first on-study SRE was 20.6 months for denosumab and 16.3 months for zoledronic acid. Denosumab was noninferior to zoledronic acid in delaying time to first on-study SRE (HR 0.84, 95% CI 0.71–0.98, $P = 0.0007$), with superiority for denosumab nearing statistical significance at a P value of 0.06. Also denosumab failed to reduce time to first and subsequent SREs significantly with an HR of 0.90 for denosumab compared with zoledronic acid (95% CI 0.77–1.04, $P = 0.14$). Overall survival and disease progression were similar between the groups. The smaller number of patients randomized and shorter time on study yielded fewer SREs in this trial compared with the similarly designed breast and prostate trials, and thus may be the reason for the less dramatic improvements with denosumab seen in this study.

Denosumab resulted in greater suppression of the urinary NTx/creatinine ratio (76% decreases in the denosumab groups versus 65% in those on zoledronic acid, $P = 0.001$). When stratified by tumor type, the HR for time to first on-study SRE for denosumab versus zoledronic acid was 0.84 (95% CI 0.64–1.10, $P = 0.20$) for non-small cell lung cancer and 0.76 for other solid tumors (95% CI 0.62–0.99, $P = 0.04$). However, the HR for the 180 patients treated with multiple myeloma was only 1.03 (95% CI 0.68–1.57, $P = 0.89$) and thus the FDA approval of denosumab is limited to patients with solid tumors and excludes treatment of patients with multiple myeloma. Pain control was monitored at baseline, day 8, and before each monthly visit patients by the Brief Pain Inventory. Patients on denosumab experienced a delay in clinically significant pain worsening compared with patients on zoledronic acid (HR 0.85, 95% CI 0.73–0.98, $P = 0.02$), with the similar rates of overall adverse events (28, 29). Hypocalcaemia occurred more frequently in the denosumab group as compared with the zoledronic acid group (10.8% versus 5.8%), including grade 3 or 4 hypocalcaemia in 20 patients (2.3%) on denosumab and nine patients (1.0%) on zoledronic acid. The rates of ONJ were similar between the two groups (11 patients (1.3%) in the zoledronic acid group versus 10 patients (1.1%) in the denosumab group) and were seen primarily in patients with known risk factors. Acute-phase reactions were more common in the zoledronic acid group (14.4% zoledronic acid versus 6.9% denosumab). Dose reduction was required in 17.3%, and 8.9% of doses were held in patients on zoledronic acid due to renal dysfunction. Despite these dose adjustments, renal dysfunction was more common in the zoledronic acid group (10.9% versus 8.3%).

The effects of denosumab versus zoledronic acid were evaluated with respect to time to first on-study SRE for noninferiority (primary endpoint) and superiority (secondary endpoint), and time to first and subsequent SRE (secondary endpoint). A total of 5723 patients were evaluated, 2861 in the zoledronic acid group and 2862 in the denosumab group. In this combined analysis,

denosumab significantly prevented or delayed the time to first on-study SRE or hypercalcaemia of malignancy, with a risk reduction of 17% (HR 0.83, 95% CI 0.76–0.90, *P* , 0.001 for both noninferiority and superiority). The median time to first on-study SRE was 27.7 months with denosumab versus 19.4 months with zoledronic acid, resulting in a median delay of 8.2 months in favor of denosumab therapy. The effect of denosumab was consistent across all types of SREs (fracture, radiation, surgery, and spinal cord compression) (30, 31).These data are summarized in table 1.

Table 1: Hazard ratios for development of SREs by type.

Type of SREs	Hazard ratio(95% CI)
Any SREs	0.83 (0.76–0.90), P= 0.001 in favor of denosumab
Pathological fracture	0.86 (0.76–0.96), P = 0.090 in favor of denosumab
Radiation to bone	0.77 (0.69–0.87), P= 0.001 in favor of denosumab
Spinal cord compression	0.89 (0.65–1.21), P = 0.45 in favor of denosumab
Surgery to bone	0.86 (0.61–1.21), P = 0.38 in favor of denosumab
Hypercalcaemia	0.63(0.41-0.98), P = 0.042 in favor of denosumab

Abbreviations: CI, confidence interval; SRE, skeletal-related events.

In addition, combined analysis from the Phase III trials in patients with metastatic breast cancer and in patients with solid tumors other than breast or prostate cancer showed a significant decrease in hypocalcaemia of malignancy in those treated with denosumab (HR 0.63, 95% CI 0.41–0.98, *P* = 0.042) (32), with similarity between two groups as regard; disease progression, overall survival and the incidence of all AEs. However, as with the individual trials, there was an increased incidence of hypocalcaemia in the denosumab group (9.6% versus 5.0%) and acute-phase reactions (20.2% versus 8.7%) in the zoledronic acid group (table 2).

Table 2; summarizes the adverse events observed in the three Phase III trials in patients with breast cancer, prostate cancer, and other solid tumors or multiple myeloma.

	Denosumab (n=2841)a	Zoledronic acid (n=2841)a
Adverse event (total)	2734(96.2%)	2745(96.8%)
Adverse event leading to study discontinuation	270 (9.5%)	280(9.9%)
CTCAE grade 3 or more	2000(70.4%)	2009(70.8%)
Adverse event of interest:		
• Acute phase reactions (first 3 days).	246(8.7%)	572(20.2%)
• Hypocalcaemia.	273(9.6%)	141(5.0%)
• Osteonecrosis of the jaw.	52(1.8%)	37(1.3%)

Note: [a] Patients who received at least one dose of active drug.
Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events

Incidence of ONJ was infrequent and similar between the treatment groups, with a cumulative incidence of 1.3 %(37 events) in the zoledronic acid group compared with 1.8% (52 events) in the denosumab group. Further safety data have been presented for denosumab use in patients with metastatic breast cancer, including patients on therapy for up to 5 years (33). In this analysis of patients from the open-label extension phase of the metastatic breast cancer registration trial, no new safety signals were observed in patients who switched from zoledronic acid to denosumab therapy or who remained on denosumab therapy for up to 5 years (median time on denosumab 19.1 months, range 0.1–59.8 months).

Future uses

The role of denosumab for the prevention of SREs in patients with bone metastasis from solid tumors has now been established in three large, well-designed, and definitive trials. Potential clinical questions include indications for and timing of transition from intravenous bisphosphonate to denosumab. Obvious indications for switching to denosumab include progressive renal insufficiency or intolerance to side effects associated with bisphosphonates.

The Phase III STAND (Study of Transitioning from AleNdronate to Denosumab) trial looked at sequential use of oral bisphosphonates followed by denosumab in postmenopausal women with primary osteoporosis (34). Postmenopausal women at least 55 years of age with lumbar spine or total hip bone mineral density measurements corresponding to a T score of -2.0 to -4.0 who had been receiving alendronate at 70 mg/week for at least 6 months were eligible. Subjects were randomized to denosumab 60 mg subcutaneously every 6 months versus continuing oral alendronate. All subjects were supplied with calcium and vitamin D supplements daily.

The primary efficacy endpoint was the percentage change in total hip bone mineral density after 12 months of therapy. Bone mineral density at the total hip increased significantly more in patients transitioned to denosumab (1.90%, 95% CI 1.61%–2.18%) compared with patients continuing on alendronate (1.05%, 95% CI 0.76%–1.34%, (*P*, 0.0001). Sequential use has also been explored in a Phase II trial in which 111 patients with solid tumors and bone metastasis previously treated with bisphosphonate were randomized to continue intravenous bisphosphonates versus switching to subcutaneous denosumab 180 mg subcutaneously every 4 or 12 weeks) (35). Urinary NTx was reduced to below 50 nmol/L by week 13 (the primary endpoint) in 71% of patients on denosumab versus 29% of patients who continued on intravenous bisphosphonates (*P*, 0.001). The percentage of patients experiencing a first on-study SRE during the 25-week treatment period was 8% in the denosumab arm versus 17% in the intravenous bisphosphonate arm (odds ratio 0.31; 95% CI 0.08–1.18). These trials suggest a role for switching to denosumab in patients who are currently receiving oral or intravenous bisphosphonates and experience a skeletal-related event or who continue to have an elevated urinary NTx level despite bisphosphonate therapy. There are currently no data to support the combined use of a bisphosphonate plus denosumab to reduce osteoclast activity further due to the risk of increased toxicity especially ONJ and hypocalcaemia.

Several trials in early-stage breast cancer patients suggest a role for bone-modifying agents in improving disease-free survival. The ABCSG-12 trial in premenopausal women with early-stage breast cancer is suggesting a role for bone-targeted therapy in the prevention of breast cancer recurrence (36). Unfortunately, the subsequent AZURE (Adjuvant Zoledronic Acid to Reduce Recurrence) trial, failed to show a similar improvement in breast cancer recurrence (37). However, in subgroup analysis, there was an improvement in both disease-free and overall survival in older women treated with zoledronic acid. There are data to suggest that RANKL may also be integral to the spread and propagation of cancer cells in bone (38). The Phase III D-CARE trial is underway to assess the effect of denosumab on disease recurrence in patients with stage II and III high-risk, early-stage breast cancer (39).

The full results the D-CARE trial will help define the role of denosumab therapy for preventing cancer progression and specifically bone metastases in patients with prostate and breast cancer.

Conflict of interest: The authors certify that is no potential or actual conflict of interest related to this article.

References

1. **Coleman R.E, Roodman S:** Clinical features of metastatic bone disease and risk of skeletal morbidity, Clinical Cancer Research, vol. 12, no. 20, pp. 2006,6243s–6249s.
2. **Rosen LS:** 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. Cancer. , 2004, 100(12): 2613–2621.
3. **Kohno N:** 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(15):3314–3321.
4. **Brown JP, Prince RL, Deal C:** Comparison of the effect of Denosumab and alendronate on BMD and biochemical markers of bone turnover in postmenopausal women with low bone mass: a randomized, blinded, phase 3 trial. J Bone Miner Res. 24(1):153–161, 2009.
5. **Roodman GD:** Mechanisms of bone metastasis. N Engl J Med, 2004, 350:1655-1664.
6. **Hofbauer LC, Neubauer A, and Heufelder AE:** Receptor activator of nuclear factor-kappaB ligand and osteoprotegerin: Potential implications for the pathogenesis and treatment of malignant bone diseases. Cancer, 2001, 92: 460-470.
7. **Selvaggi G, Scagliotti GV:** Management of bone metastases in cancer: A review. Crit Rev Oncol Hematol , 2005,56:365-378.
8. **Coleman RE, Major P, Lipton A:** 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.
9. **Brown JE, Cook RJ, and Major P:** Bone turnover markers as predictors of skeletal complications in prostate cancer, lung cancer, and other solid tumors. J Natl Cancer Inst, 2005, 97: 59-69.
10. **Bekker PJ, Holloway DL, and Rasmussen AS:** A single-dose placebo controlled study of AMG 162, a fully human monoclonal antibody to RANKL, in postmenopausal women. J Bone Miner Res. 2005, 20 (12): 2275–2282.
11. **Cummings SR, San Martin J, McClung MR:** Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009361(8):756–765.
12. **Brown JP, Prince RL, Deal C:** Comparison of the effect of Denosumab and alendronate on BMD and biochemical markers of bone turnover in postmenopausal women with low bone mass: a randomized, blinded, phase 3 trial. J Bone Miner Res, 2009 24(1):153–161.
13. **Ellis GK, Bone HG, Chlebowski R:** Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for nonmetastatic breast cancer. J Clin Oncol. , 2008, 26(30):4875–4882.
14. **Smith MR, Egerdie B, Herngndez Toriz N:** Denosumab in men receiving androgen-deprivation therapy for prostate cancer. N Engl JMed. 2009, 361(8):745–755.
15. **Xgeva® [package insert]. Thousand Oaks, CA:** Amgen Inc; 2010.
16. **(Tabrizi MA, Tseng CM, Roskos LE:** Elimination mechanism of therapeutic monoclonal antibodies. Drug Discov Today, 2006, 11(1–2): 81–88.
17. **Kong YY, Yoshida H, Sarosi I:** OPGL is a key regulator of osteoclastogenesis, lymphocyte development and lymph-node organogenesis. Nature. 1999, 397(6717):315–323.
18. **Miller PD, Wagman RB, and Peacock M:** Effect of denosumab on bone mineral density and biochemical markers of bone turnover: six year results of a phase 2 clinical trial. J Clin Endocrinal Metab. 2011, 96(2):394–402.
19. **Stopeck A, Martin M, Ritchie D:** Effect of denosumab versus zoledronic acid treatment in patients with breast cancer and bone metastases: results from the extended blinded treatment phase. Abstract P6-14-01, presented at San Antonio Breast Cancer Symposium, December 8–12, 2010, San Antonio, TX.
20. **Smith MR, Egerdie B, Hernández Toriz N:** Denosumab in men receiving androgen-deprivation therapy for prostate cancer. N Engl J Med. 2009; 361(8):745–755.
21. **Stopeck A, Lipton A, Campbell-Baird C:** Acute-phase reaction following treatment with zoledronic acid or denosumab: results from a randomized, controlled phase 3 Study in patients with breast cancer and bone metastases. Abstract P6-14-09, presented at San Antonio Breast Cancer Symposium, December 8–12, 2010, San Antonio, TX.
22. **Fallowfield L, Patrick D, Body J:** Effects of denosumab versus zoledronic acid (ZA) on health-related quality of life (HRQL) in metastatic breast cancer: Results from a randomized phase III trial. Abstract number 1025, presented at the ASCO annual meeting, June 4–8, 2010, Chicago, IL.
23. **Van Poznak CH, Temin S, Yee GC:** American Society of Clinical Oncology executive summary of the clinical practice guideline update on the role of bone-modifying agents in metastatic breast cancer. *J Clin Oncol*. 2011; 29(16):1221–1227.
24. **Lipton A, Steger CG, Figueroa J:** Randomized active-controlled phase II study of denosumab efficacy and safety in patients with breast cancer related bone metastases. *J Clin Oncol*. 2001; 25(28):4431–4437.
25. **Tabrizi MA, Tseng CM, Roskos LE:** Elimination mechanism of therapeutic monoclonal antibodies. *Drug Discov Today*. 2006; 11(1–2): 81–88.
26. **Kong YY, Yoshida H, Sarosi I:** OPGL is a key regulator of osteoclastogenesis, lymphocyte development and lymph-node organogenesis. *Nature*. 1999; 397(6717):315–323.
27. **Henry DH, Costa L, Goldwasser F:** 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. 2001; 29(9):1125–1132
28. **Richardson GE, Ciuleanu TE, and Costa L:** Denosumab versus zoledronic acid in patients with bone metastases from solid tumors other than breast and prostate cancers or multiple myeloma: A number needed to treat (NNT) analysis. Abstract number 9115, presented at the ASCO annual meeting, June 3–7, 2011, Chicago, IL.
29. **Von Moos R, Patrick D, Fallowfield L:** Effects of denosumab versus zoledronic acid on pain in patients with advanced cancer (excluding breast and prostate) or multiple myeloma: Results from a randomized phase III clinical trial. Abstract number 9043, presented at the ASCO annual meeting, June 4–8, 2010, Chicago, IL.
30. **Lipton A, Fizazi K, Stopeck A:** Prevention of skeletal-related events with denosumab or zoledronic acid: combined analysis from 3 registrational trials. Abstract number 3061, presented at the European Multidisciplinary Cancer Congress, September 23–27, 2011, Stockholm, Sweden.
31. **Diel IJ, Body JJ, Stopeck A:** Effect of denosumab treatment on prevention of hypercalcemia of malignancy in cancer patients with bone metastasis. Abstract number 3051, presented at the European Multidisciplinary Cancer Congress, September 23–27, 2011, Stockholm, Sweden.
32. **Saad F, Brown JE, Van Poznak C:** Incidence, risk factors, and outcomes of osteonecrosis of the jaw: integrated analysis from three blinded active controlled phase III trials in cancer patients with bone metastases. *Ann Oncol*. 2011. Epub Oct 10.

33. **Stopeck AT, Lipton A, Martin M:** Denosumab in patients with breast cancer and bone metastases previously treated with zoledronic acid or denosumab: results from the 2-year open-label extension treatment phase of a pivotal phase 3 study. Abstract P3-16-07, presented at the San Antonio Breast Cancer Symposium, December 6–10, 2011, San Antonio, TX.
34. **Kendler DL, Roux C, Benhamou CL:** Effects of denosumab on bone mineral density and bone turnover in postmenopausal women transitioning from alendronate therapy. *J Bone Miner Res*. 2010; 25(1): 72–81.
35. **Fizazi K, Lipton A, Mariette X:** Randomized Phase II trial of denosumab in patients with one metastases from prostate cancer, breast cancer, or other neoplasms after intravenous bisphosphonates. *J Clin Oncol*. 2009; 27(10):1564–1571.
36. **Gnant M, Mineritsch B, Schippinger W:** Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *N Engl J Med*. 2009; 360(22):679–691.
37. **Coleman RE, Marshall H, Cameron D:** Breast-cancer adjuvant therapy with zoledronic acid. *N Engl J Med*. 2011; 365(15):1397–1405.
38. **Jones DH, Nakashima T, Sanchez OH:** Regulation of cancer cell migration and bone metastasis by RANKL. *Nature*. 2006; 440(7084): 692–696.
39. **Study of denosumab as adjuvant treatment for women with high risk early breast cancer receiving neoadjuvant or adjuvant therapy (D-CARE).** Available from: http://clinicaltrials.gov/ct2/show/NCT01077154. Accessed December 15, 2011.